Improving Sleep and Cognition in Young Adults and the Elderly

Thesis (cumulative thesis)

Presented to the Faculty of Arts and Social Science

of the University of Zurich

for the Degree of Doctor of Philosophy

by

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Accepted in the Autumn Term 2014

on the Recommendation of the Doctoral Committee:

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Zürich, 2014

"It is this potential for plasticity of the relatively stereotyped units of the nervous system that endows each of us with our individuality."

- *Eric Kandel, Principles of Neural Science* -

Acknowledgements

I would like to thank Prof. Dr. Björn Rasch for giving me the opportunity to write this thesis in his lab of Biopsychology. I particularly appreciate his supportive and motivating nature and his enthusiasm, which inspired the creation of my own ideas and interests, the implementation of which he kindly supported.

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I also want to thank Prof. Dr. Mike Martin for acting as a second supervisor and providing me with some gerontopsychological background and essential organizational information.

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I thank my colleagues for the very friendly and supportive working environment and for having an enjoyable time during conferences. I am also grateful for the support of the Master Students and interns who accompanied me and spent hours and hours in the sleep lab to help me find answers to my research questions.

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Finally, I would like to thank my family, partner and friends for their love and care, establishing a safe and stable background. Thanks for your support and for taking off some of the pressure.

Abstract

Sleep, particularly slow-wave sleep (SWS), is a critical factor for health and well-being. Furthermore, SWS provides a brain state supportive for the spontaneous reactivation, stabilization, and long-term storage of declarative memories. Sleep architecture changes across lifespan and the parallel nascent impairments in SWS, cognition, and other health aspects hint at a deteriorating interplay between these three factors. Thus, a profound understanding of the nature of the relationship between sleep and memory in young and old human participants is fundamental in successfully finding new ways of memory- and sleep-related interventions.

The first study was designed to clarify the role of induced reactivations for memory consolidation during sleep in different sleep stages. While reactivation during SWS has been reported to improve memory and stabilize it against future interference, the role of reactivations during rapid eye movement (REM) sleep is less clear. On the one hand, spontaneous reactivations, functionally associated with memory performance, exist in REM sleep. On the other hand, declarative memories have proven stable after sleep which is free from REM sleep. As induction of memory reactivations during REM sleep failed to shelter memory from interference, we concluded that spontaneous reactivations which appear during REM sleep do not contribute to the stabilization of declarative memories.

The second study tested hypnosis as a tool to objectively improve sleep as its efficacy had previously been proven for subjective sleep measures. Our data was the first to confirm this effectiveness on an objective level by revealing a specific increase in SWS and slow-wave activity (SWA) amounts after hypnotic suggestions to deepen sleep in younger adults. Contrary to expectations, SWS-enriched sleep by hypnosis did not improve memory consolidation.

As sleep improvements are particularly critical in advanced age, but generalizations from results of younger adults to older adults are not valid, we replicated the study in the third manuscript with older adults. Hypnotic suggestions again proved effective in increasing the amounts of SWS and SWA. Cognition associated with prefrontal activity benefited from this increase. Results for memory consolidation were less pronounced, but promising. Together, data indicated an age-independent effect of hypnotic suggestions on SWS enrichment. They further supported the assumption that SWS restores prefrontal cortex (PFC) functionality and benefits consolidation. As an outlook, hypnotic suggestions to increase SWS might be combined with induced memory reactivations during this sleep stage to further improve memory consolidation processes in the elderly.

Together, the manuscripts in this thesis investigate the relationship between sleep and memory on a theoretical and a practical level. One study clarifies the role of REM sleep reactivations for memory stability and two studies confirm the effectiveness of hypnotic suggestions to objectively

increase SWS and SWA independent of age. Owing to these insights, the recommendation of hypnosis as a non-pharmacological technique to improve sleep depth, subjective sleep quality and to positively influence cognitive abilities in older adults can be based on objective and experimentally controlled data. There is great potential inherent in this line of research, which paves the way to positively influence senescence processes in major areas of life and health.

Zusammenfassung

Schlaf, vor allem Tiefschlaf (SWS), trägt entscheidend zu Gesundheit und Wohlbefinden bei. Darüber hinaus unterstützt Tiefschlaf spontane Reaktivierungen, sowie die Stabilisierung und Langzeitspeicherung von deklarativen Gedächtnisinhalten. Die Schlafstruktur verändert sich über die Lebensspanne hinweg und die dabei parallel auftretenden Beeinträchtigungen des Tiefschlafs, der Kognition und anderer Gesundheitsaspekte deuten auf ein zerstörerisches Zusammenspiel zwischen diesen drei Faktoren hin. Daher ist ein tiefgreifendes Verständnis des Wesens der Beziehung zwischen Schlaf und Gedächtnis bei jüngeren und älteren Menschen grundlegend, um erfolgreich neue Interventionsmöglichkeiten zu finden.

Die erste Studie wurde konzipiert, um die Rolle induzierter Gedächtnisreaktivierungen auf die Konsolidierung im Schlaf während verschiedener Schlafstufen zu klären. Einerseits treten spontane Reaktivierungen, die funktional für die Gedächtnisleistung sind, auch im REM (Rapid Eye Movement) Schlaf auf. Andererseits zeigte sich auch nach einem Schlaf ohne REM Anteil eine Stabilisierung des deklarativen Gedächtnisses. Da die Induktion von Gedächtnisreaktivierungen während des REM Schlafs das Gedächtnis nicht vor Interferenz zu schützen vermochte, schlossen wir auf einen mangelnden Beitrag der Reaktivierungen im REM Schlaf zur Gedächtnisstabilisierung deklarativer Inhalte.

Die zweite Studie testete Hypnose als Methode zur Verbesserung des Schlafs, da dessen Wirksamkeit zuvor für subjektive Schlafmaße bestätigt werden konnte. Unsere Daten bestätigten diese Wirksamkeit erstmals an objektiven Maßen, indem sie einen spezifischen Anstieg im Tiefschlafanteil und der Tiefschlafaktivität (SWA) nach einer hypnotischen Suggestion „tiefer zu schlafen“ bei jüngeren Erwachsenen aufwiesen. Entgegen der Erwartung verbesserte der durch Hypnose vertiefte Schlaf die Gedächtniskonsolidierung nicht.

Da Verbesserungen des Schlafs besonders im fortgeschrittenen Alter relevant sind, aber Generalisierungen der Ergebnisse von jüngeren auf ältere Erwachsene nicht valide sind, replizierten wir die Studie mit älteren Erwachsenen im dritten Manuskript. Die hypnotischen Suggestionen erwiesen sich abermals als förderlich für SWS und SWA. Des Weiteren war die Leistung bei präfrontal abhängigen Gedächtnisaufgaben verbessert. Die Effekte für die Gedächtniskonsolidierung waren geringer, aber vielversprechend. Insgesamt deuteten die Daten auf einen altersunabhängigen Effekt der hypnotischen Suggestionen auf die Tiefschlaferweiterung hin. Sie unterstützen außerdem die Annahme, dass Tiefschlaf präfrontale Areale funktional restauriert und der Gedächtniskonsolidierung zu Gute kommt. Für künftige Studien wird vorgeschlagen, hypnotische Suggestionen zur Vertiefung des Schlafs mit der Induktion von Gedächtnisreaktivierungen während dieser Schlafstufe zu kombinieren, um die Gedächtniskonsolidierung bei älteren Erwachsenen weiter zu verbessern.

Zusammenfassend untersuchen die drei Manuskripte dieser Dissertation die Beziehung zwischen Schlaf und Gedächtnis auf der theoretischen und der praktischen Ebene. Eine Studie klärt die Rolle von Reaktivierungen im REM Schlaf für die Festigung deklarativer Gedächtnisinhalte und zwei Studien bezeugen die altersunabhängige Wirksamkeit hypnotischer Suggestionen zur Erhöhung von SWS und SWA anhand polysomnographischer Daten. Dank dieser Erkenntnisse kann die Empfehlung, Hypnose als nichtmedikamentöse Technik zu nutzen, um den Schlaf zu vertiefen, subjektive Schlafqualität zu erhöhen und kognitive Fähigkeiten bei älteren Erwachsenen positiv zu beeinflussen auf objektiv und experimentell kontrollierte Daten gestützt werden. Dieser Forschungssparte wohnt ein großes Potential inne, Altersprozesse in wesentlichen Bereichen des Lebens und der Gesundheit positiv zu beeinflussen.

Index of Content

Index of Figures

Index of Tables

1. Introduction

Recalling the past, learning and adapting from experience are central to our existence and recognition of ourselves as coherent entities persisting over time. Meanwhile we are aware of our memory's selectivity and vulnerability, which become even more pronounced across lifespan. This decline parallels other age-related impairments in health, subjectively experienced quality of life and sleep. Critically, learning, recall, and the process of storing newly learned information particularly benefit from sleep. It is still unclear which sleep stages or which of their components facilitate which aspect of memory. For instance, the role of rapid eye movement (REM) sleep for memory stabilization has not yet been clarified. Nevertheless, the critical contribution of the deepest sleep stage, slow-wave sleep (SWS), to cognition, but also to general health and well-being is evident. Unfortunately, this component decreases dramatically as a function of age. Because of this association, there is good reason to focus on deep sleep when striving for the maintenance of high level cognitive function and good health or when targeting senescence. Sleep as an automatic process can, however, hardly be influenced wittingly and is therefore mostly treated with medication, which can entail unwanted side effects. Alternatively, hypnotherapy has proven effective in influencing certain subjectively rated sleep parameters. Objective evidence as measured by polysomnography still needs to confirm these promising findings. If effective, hypnosis could be used as a risk-free and non-pharmacological tool to improve sleep quality and to treat age-related and possibly even clinically relevant sleep problems. Improving nocturnal restoration might have a beneficial influence on aspects of health and cognition. Thus, this approach could reveal a technique applicable to improve sleep and cognitive abilities in young adults and the elderly.

The following sections build up a theoretical framework of memory, sleep, and their interrelationship from a theoretical and practical perspective. In the course of this conceptual introduction, key concepts, research gaps, and prospects will be illustrated. Afterwards, the methods used in the manuscripts will be presented, i.e., the induction of memory reactivations as a method to test their functionality and hypnosis as a non-pharmacological approach to improve sleep. Three main hypotheses will be constructed for the gaping holes in research which will be investigated in the following manuscripts.

1.1. Memory

The first chapter is about memory, the ability to encode, store, and recall information. The section is divided into three paragraphs focusing on the basic introduction and definition of memory

formation and its subsystems. Next, age-related changes in memory and the brain structures involved in memory processes will be outlined.

1.1.1. Memory formation: encoding, consolidation, retrieval

In order to understand the main processes involved in memory, this paragraph will introduce the three stages of memory formation: encoding, consolidation, and retrieval. During encoding, sensory information from the environment is acquired, processed, and converted into a mental representation. Memory traces for this construct are created to enable later recall from short- or long-term memory. Encoding can occur in every modality, be intentional or incidental, including or bypassing conscious processes. Further, it can be deep or shallow, that is, engaging in finding associations to previous knowledge or not. After learning, memories must be stored. The two stage model postulates two memory stores: short-term memory, rapidly storing a limited amount of items for a limited time period and a long-term memory store in which these items must be transferred to persist over time. This transfer is called consolidation and describes the process in which the labile, freshly encoded memories are strengthened and bound into the established network of pre-existing knowledge to become stabilized over time (Diekelmann & Born, 2010; McGaugh, 2000; Squire, Cohen, & Nadel, 1984). Neurologically, synapses grow during consolidation to increase the number of signals they can transfer to other neurons. The potential to change synaptic strength is called synaptic plasticity and represents the basis of memory formation. To achieve resistance to interference, memories are redistributed and reorganized during consolidation. After encoding, memories initially depend on the hippocampus and on modality-specific cortical areas (Frankland & Bontempi, 2005). The hippocampus thereby acts a link between the single aspects of the memory which are distributed across the neocortex (Squire & Zola, 1996). During recall and in the course of consolidation, these hippocampal-neocortical connections are repeatedly activated simultaneously, which binds them strongly together. Increasing repetition strengthens also the cortico-cortico connections and reduces the need for hippocampal activation to connect these aspects. Hence, over time, activating any of these aspects can activate the whole network without hippocampal involvement (Squire et al., 1984). This is reflected in findings that the hippocampus is necessary for learning and recalling new memories, while the neocortex becomes more and more sufficient for recollection of remote memories (McGaugh, 2000; Squire et al., 1984). Thus, on a structural level, consolidation is associated with a transfer of memories from medial temporal lobe structures, particularly the hippocampus, into neocortical structures (Frankland & Bontempi, 2005; McClelland, McNaughton, & O'Reilly, 1995). Besides the initial involvement of the hippocampus, prefrontal structures are recruited for controlled processing during retrieval, i.e., the access to stored

information (Buckner, 2004; Squire et al., 1984). During recall, the brain replays the same neuronal activity that was initiated during learning. After activation of memory traces by retrieval, memories re-enter a labile state and need to be reconsolidated. This means that another series of active consolidation takes place after recall. This process strengthens memories even more for long-term storage.

Thus, successful memory formation encompasses encoding and consolidation which allow renewed access to the learned material during retrieval. However, memory is not a unitary system, but can be decomposed into different subsystems which will be defined in the following section.

1.1.2. Memory systems: procedural vs. declarative memory

Tulving (1985) defined two memory systems which will be outlined in the following. Although not considered fully independent of each other, he differentiated between procedural and declarative memory. Procedural memory ("knowing how") arises from implicit learning such as priming or conditioning. It involves the acquisition of diverse skills such as riding a bike or playing the piano, mainly through repetition and practice. Procedural memory refers to reactions, learned and executed without any or very low levels of conscious recollection, reflection, or intent. Involvement of hippocampal structures is not needed, but brain areas that are involved in the execution of the respective actions or procedures are activated besides basal ganglia and cerebellum (Cohen & Eichenbaum, 1994; Heindel, Butters, & Salmon, 1984). This thesis, however, deals particularly with declarative memory ("knowing what"). Encoding and retrieval of declarative material requires consciousness and intent together with the awareness of the internal and external world. Declarative memory is further sub-divided into semantic and episodic memory. The former represents structured knowledge of learned facts and concepts like capitals of countries, functions of objects, names, or meanings of words. Episodic memory subsumes the aware recollection of personal experiences and specific events together with their surrounding context. Elements of both systems, semantic and episodic, must be retrieved consciously and explicitly during an active recall. Memories initially strongly depend on the medial temporal lobe, particularly on the hippocampus. However, they are gradually reorganized over time and become increasingly dependent on cortical areas (Frankland & Bontempi, 2005).

Although a clear-cut separation between both systems is neither theoretically (Tulving, 1993) nor practically possible (Peigneux, Laureys, Delbeuck, & Maquet, 2001), declarative and procedural memories are differentiated and usually investigated separately. For this purpose, tasks have been designed to represent the underlying theoretical memory system as closely as possible. For the investigation of procedural memory, motor tasks are usually applied, for example a finger tapping

task which requires quick and correct typing of a numerical sequence displayed on a screen. To investigate declarative memory, word pair learning with cued recall or visual-spatial learning tasks are frequently used. The need for a differentiation between systems also becomes obvious when considering their susceptibility to aging as will be described in the following.

1.1.3. Age-related changes in memory and brain structure

Assessing memory performance demonstrates that unlike procedural memory, declarative memory shows age-related declines. Younger adults outperform older adults in almost all sorts of memory tasks (Head, Rodrigue, Kennedy, & Raz, 2008; Luo & Craik, 2008; Mitchell, Brown, & Murphy, 1990). Despite its theoretical infinity (Wheeler, Stuss, & Tulving, 1997), episodic memory is particularly susceptible to loss and forgetting (Tulving, 1972). This becomes evident in the preeminence of younger adult's performance in episodic memory tasks over older adults' (Ayanna, Thomas & Bulevich, 2006; Brehmer, Li, Müller, von Oertzen, & Lindenberger, 2007; Mitchell et al., 1990). This age decrement appears in recognition tasks as well as in free recall performance (Craik & McDowd, 1987). Aging researchers attribute factors such as the reduction of processing speed (T.A. Salthouse, 1980; Timothy A. Salthouse, 1996) or inhibitory functions (Persad, Abeles, Zacks, & Denburg, 2002) to this decline. Besides this, shrinking attentional resources (Craik, Routh, & Broadbent, 1983) or processing control (Jennings & Jacoby, 1993) were discussed as factors having an impact. Although plausible and able to explain some of the findings, none of these factors has yet satisfactorily explained the memory decline. However, taken together, reasons for the memory impairments are often linked to reduced executive functioning (Troyer, Graves, & Cullum, 1994). Due to the dependence of executive functions on prefrontal brain structures, fronto-striatal circuits are as important for memory function as medial temporal lobe structures. Unfortunately, both the prefrontal cortex (PFC) and the hippocampus are specifically prone to age-related brain atrophy (Hedden & Gabrieli, 2004). This is as true for white as for gray matter (Head, 2004; Salat et al., 2004). Interestingly, their shrinkage is correlated to a degree that suggests a common pathological process (N. Raz et al., 2005). Their atrophy affects memory however differently. While brain matter reductions in the hippocampus impair declarative memory performance directly, changes in frontal-striatal circuits indirectly exert a deteriorating influence on acquisition and recall performance by limiting working memory and executive control (Head et al., 2008; Parkin & Walter, 1991; Squire, Stark, & Clark, 2004). It must however also be noted that brain matter changes are not always related to cognitive impairments. The individual response to atrophy can range from compensation to system breakdown (Buckner, 2004). For instance, similar performance levels in younger and older adults often go along with greater recruitment of frontal brain areas in elderly compared to younger

adults. This over-recruitment of frontal areas was interpreted as a compensatory mechanism (Spreng, Wojtowicz, & Grady, 2010). Similar findings of increased responses of prefrontal cortex to verbal learning were reported in sleep-deprived younger adults (Drummond et al., 2000), supporting the assumption of over-recruitment as a compensatory mechanism. This data not only highlights the importance of prefrontal functions for memory performance, but also brings the role of sleep for memory into play.

1.1.4. Interim summary

Memory formation includes three stages: encoding, consolidation, and retrieval. The memory system is sub-divided into procedural and declarative memory, distinguished according to the learning content and required degree of consciousness during learning and recall. Age-related impairments are particularly observable in declarative memory performance and result from multiple neuronal and cognitive declines (Head et al., 2008). Besides physical integrity and functionality of brain structures, other factors influence executive functioning and memory performance. One of these is sleep. Before going into the details on the relationship between sleep and memory, the brain state "sleep", in which humans spend about one third of their lifetime, will be elaborated closely.

1.2. Sleep

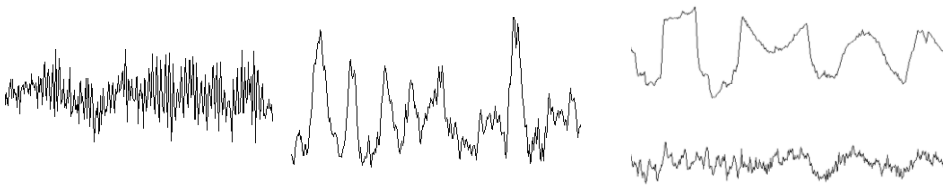
Sleep is defined as "a reversible behavioral state of perceptual disengagement from and unresponsiveness to the environment" (Carskadon & Dement, 2000, p.15), connoting a loss of consciousness to this state. It occurs naturally at regular intervals ranging from 6 to 9 hours per night in a healthy sleeper. Increasingly detailed knowledge about sleep has only been gained over the last few decades, more precisely, after the development of the electroencephalography (EEG) as first described in 1929 (H. Berger, 1929). Only afterwards could physiological processes during sleep be measured and systematically investigated, which objectified its distinction from wakefulness. Up to now, the EEG is the first-choice tool to examine sleep and to decompose it to its basics according to the patterns of electrical activity appearing in the EEG signal. Complemented with measures of eye movement (electrooculography, EOG) and muscle tone (electromyography, EMG), collectively termed polysomnography (PSG), sleep can be characterized. Its components are described in the first of the following sections. However, as the nature of sleep changes as a function of age, the most important sleep characteristics of an elderly person will be highlighted in the second part. Finally, the functions of this brain state will be outlined, culminating in its outstanding importance for memory.

1.2.1. Sleep architecture - sleep stages and their characteristics

Sleep can be classified into two major sleep phases which cyclically alternate across the night in roughly 90 minute cycles: rapid eye movement (REM) sleep and NonREM sleep. Within this ultradian cyclicality, the ratio of REM and NonREM sleep changes across the night. The first hours of sleep are predominated by NonREM sleep while REM sleep prevails during late sleep. According to the degree of cortical synchronization, NonREM sleep is further decomposed into stages N1, N2, and N3 (Iber, Ancoli-Israel, Chessonn, & Quan, 2007). N1 characterizes the transition from wakefulness to sleep. EEG activity begins to slow down from alpha activity (8 - 13 Hz) to a mixed frequency activity and covers about 2-5% of nocturnal sleep (Gross & Mink, 2014). N2 is characterized by phasic electrical events, such as K-complexes and sleep spindles. The former appear as large, well-delineated negative waves followed by positive amplitudes clearly distinguishable among the otherwise low-amplitudinal, mixed frequency EEG pattern. Spindles are short (> 0.5 seconds), distinct bursts of fast frequency (11 - 15 Hz). With 45-55% of N2 per night, it makes up the predominant sleep stage (Gross & Mink, 2014). N3, also known as slow-wave sleep (SWS) is the deepest stage, named according to the prevalent slow waves visible in the EEG signal. These slow oscillations result from large, synchronized neuronal assemblies, commonly alternating between silence and activity (Steriade, Contreras, Curró Dossi, & Nuñez, 1993). The common hyperpolarization (down state) and depolarization (up state) phases generate oscillations of high amplitude (> 75 µV) and low frequency (0.5 - 4.5 Hz) in EEG recorded field potentials (Iber et al., 2007). This electroencephalographic pattern is responsible for spectral power density maxima in slow oscillatory (0.5 -1 Hz) and delta (1 - 4.5Hz) frequency ranges (Achermann & Borbély, 1997), together referred to as slow-wave activity (SWA, 0.5 - 4.5 Hz). The power of oscillations and frequencies is an analogous, but more accurate measure of visually scored sleep stages (Hobson & Pace-Schott, 2002). The remaining 20 - 25% of sleep are made up with REM sleep (Dijk, 2009), which is hallmarked by large, irregular, and rapid bursts of eye movements, accompanied by a low muscle tone. Brain activity is characterized by low amplitudes and desynchronized fast theta activity (4 - 8 Hz) (Diekelmann & Born, 2010). In animals, phasic, endogenous ponto-geniculo-occipital (PGO) waves are expressed in the pons, geniculate nuclei of the thalamus and the occipital cortex, as their name implies. In human EEG they are not identifiable, but the existence of similar processes was reported. These waves activate diverse brain areas during REM sleep and are associated with the characteristic ocular activity (Peigneux, Laureys, Fuchs, et al., 2001). Since some of its features resemble waking activity rather than sleep, REM sleep is also known as paradoxical sleep. Associated with the activity of the brain during REM sleep, dreams most frequently occur in this sleep stage and appear most intense, vivid, and emotional (Gross & Mink, 2014; Hobson & Pace-Schott, 2002; Stickgold, 2005).

Besides the differences detectable in the EEG signal, sleep stages differ in brain activation (Maquet, 1995, 2000) and neurochemistry (Diekelmann & Born, 2010; Stickgold, Hobson, Fosse, & Fosse, 2001)(for details see Table 1). Sleep is characterized by a general deactivation of brain activity, blood flow, and metabolism compared to waking, although during REM sleep particularly limbic structures experience wake-like activation (Stickgold et al., 2001). Acetylcholine (ACh) and cortisol levels decrease to a minimum during NonREM while accelerate during waking and REM sleep. In contrast, Noradrenaline and serotonin are highest during waking, intermediate in SWS and lowest in REM sleep (Diekelmann & Born, 2010).

Table 1. Differences Between the Brain States

parameter	Wake	SWS	REM sleep
EEG signal			
Visual identification (REM: EOG and EEG)			
Prevalent frequency	8-13 Hz	0.5-4.5 Hz	4.5-8 Hz
Synchronicity	low	high	low
Eye movements	high	low	high
Muscle tone	high	intermediate	lowest
Brain activation			
Frontal activation	high	low	low
Limbic activations	high	low	high
Neurochemistry			
Acetylcholine	high	minimum	high
Noradrenaline	high	intermediate	minimum
Serotonin	high	intermediate	minimum
Cortisol	high (morning)	minimum	increasing
Cerebral blood flow			
Frontal	high	lowest	Intermediate
Limbic system	high	low	increased
Metabolism	high	low	high
Body temperature	high	lowest	low
Cognition	conscious thought	thought-like dreams	vivid, emotional dreaming

Notes. The table summarizes the differences between the main brain states along several dimensions. Adapted from Stickgold et al. (2001) Sleep, learning, and dreams: Off-line memory reprocessing. *SCIENCE*, 294 (5544), 1052-1057 and extended (R. Berger & Phillips, 1995; Diekelmann & Born, 2010; Hobson & Pace-Schott, 2002; Maquet, 1995, 2000). Graphics were taken from the author's own data.

1.2.2. Age-related changes in sleep

With advancing age, impairments in sleep become quite common rather than unusual (Foley et al., 1995). This is due to the fact that even healthy sleep is subjected to considerable quantitative and qualitative changes across lifespan. A meta-analysis of Ohayon et al. (2004) summarized the changes identified in a total of 65 studies including objective sleep measures of 3,577 healthy subjects, aged 5 to 102 years. All of the parameters studied changed across age: On the one hand, with increasing age, sleep latency, percentage of light sleep stages N1 and N2, and time awake after initial sleep onset (WASO) increased. On the other hand, total sleep time, percentage of SWS and REM sleep, REM latency and sleep efficiency decreased (see Figure 1). Compared to other factors influencing the amount of SWS, effect size of aging was the greatest (Ohayon et al., 2004).

Figure 1. Age-related Changes in Sleep Architecture

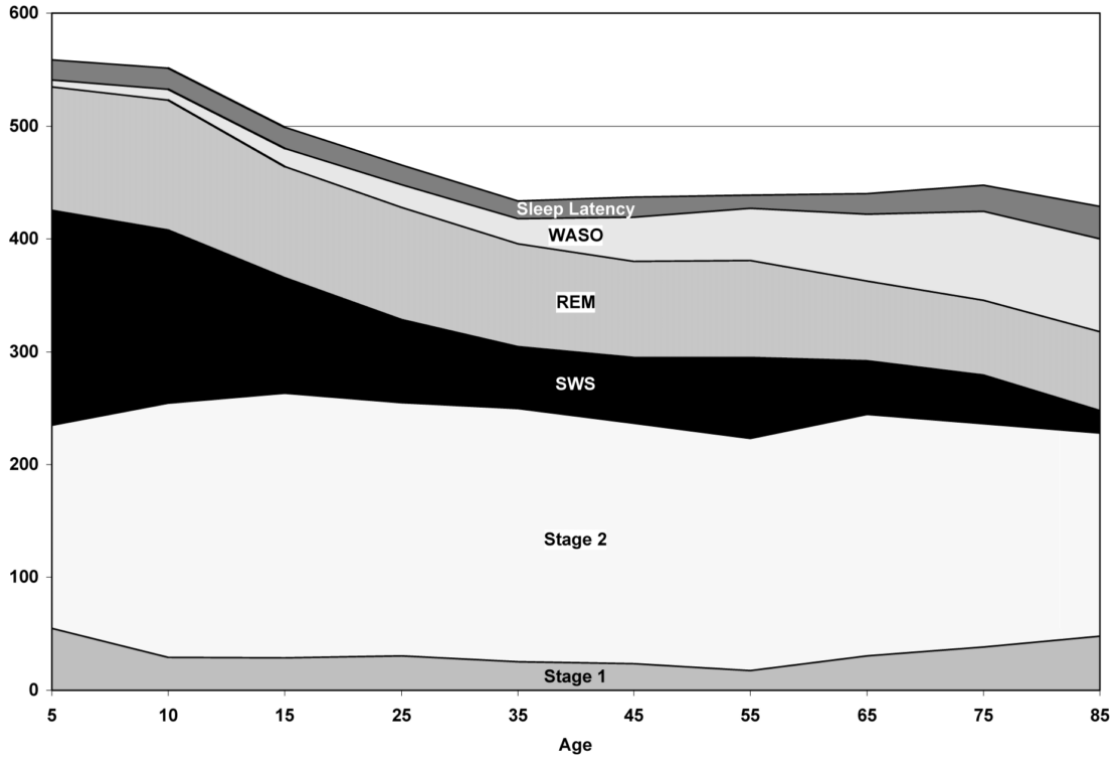


Figure 1. Taken from Ohayon et al. (2004). The figure shows the changes in sleep architecture across lifespan. While light sleep stages (e.g., Stage 1, Stage 2), sleep latency, and wake after sleep onset (WASO) increase, amounts of SWS and REM sleep decrease together with total sleep time.

On a more finely-tuned level, the comparison of EEG spectral power in night-time sleep of younger and older adults shows reduced SWA levels in the elderly (Cajochen, Münch, Knoblauch, Blatter, & Wirz-Justice, 2006). The power density in the delta band is reduced already in middle aged

men (Dijk, Beersma, & van den Hoofdakker, 1989) and its reductions are particularly dominant in frontal recording sites (Münch et al., 2004).

Together, even in healthy aging, sleep naturally becomes more fragmented, shorter, and less deep across lifespan (Van Cauter, 2000). Although this development is not necessarily associated with sleep complaints or clinical sleep disorders, it might entail diverse risks for health and cognition (Dijk, 2009). This becomes evident when considering the functions of sleep.

1.2.3. Functions of sleep and significance of SWS

The scientific search for answers as to why sleep occurs exposed the importance of sleep for body functions, such as the immune system (Lange, Dimitrov, & Born, 2010), tissue restoration (K. Adam & Oswald, 1977), and energy conservation via downward regulation of core body temperature and metabolic rate (R. J. Berger & Phillips, 1995). People with insomnia complain about more multiple than single health problems, as well as permanent rather than temporary ones, and have been hospitalized more often than good sleepers (Bixler, Kales, Soldatos, Kales, & Healey, 1979). Chronic poor sleep has been related to negative influences on psychological and physiological well-being and the impairment of waking functions (Pallesen, Nordhus, & Kvale, 1998) up to associations with risks of Alzheimer`s disease (Ju et al., 2013). Vice versa, major illnesses like depression, heart disease, or bodily pains are often comorbid with sleep disturbances (Roberts, Shema, & Kaplan, 1999), which is also reflected in the association between the amount of medical conditions and the perceived sleep quality. According to analyses of several studies, older adults' sleep and their general physical health status are also strongly related (Foley et al., 1995; Foley, Ancoli-Israel, Britz, & Walsh, 2004; McCrae et al., 2005; Roberts et al., 1999). Only 20 % of over 9 000 adults older than 65 reported none or hardly any sleep complaints in an epidemiologic study in the U.S. The complaints that were mentioned were related to poorer self-rated mental, physical, and behavioral health (e.g., intake of medication, alcohol abuse, smoking, etc.) (Goldman et al., 2007), and higher mortality (Ancoli-Israel, 2009). Another study investigated the predictive power of EEG analyses of older adults' sleep for survival time and dramatically illustrated the need for interventions protecting certain aspects of sleep in the elderly. Extended sleep latencies, low sleep efficiency, and extremely high and low percentages of REM sleep increased risk of death up to 2.14 times (Dew, 2003). Even a reduction in sleep depth by SWS deprivation is enough to lower the pain threshold in middle-aged women (Lentz, Landis, Rothermel, & Shaver, 1999) and elicit reduced glucose tolerance, increasing the risk of type 2 diabetes (Tasali, Leproult, Ehrmann, & Van Cauter, 2008). In rabbits it was shown that animals reacting on an infection with elevated levels of SWS had a higher chance of surviving the microbiological challenge (Toth, Tolley, & Krueger, 1993). Such results uncover sleep, especially SWS,

as a primary factor for healthy aging. Apart from its relevance for mental and physical health, sleep, and especially sleep depth expressed as SWS, contributes to subjective well-being. The amount of slow-wave sleep has proven to be an important determinant of daytime sleep propensity (Dijk, Groeger, Stanley, & Deacon, 2010), subjectively reported sleep quality (Akerstedt, Hume, Minors, & Waterhouse, 1997), and alertness (Lentz et al., 1999) and is thus considered the most restful sleep stage (Dijk, 2009). Finally, although the underlying mechanisms are still not fully understood, it was discovered that sleep and particularly slow-wave sleep benefit memory functioning (for review, see Rasch & Born, 2013). Studies also confirmed for older adults that besides poor health and body function, consequences of their poor sleep include impaired cognitive functions (Blackwell et al., 2006). As this intertwining is however quite complex and multidimensional and principally represents the heart of the present thesis, a much closer look at its nature will be presented at large in the following sections.

1.2.4. Interim summary

Taken together, sleep is a brain state including a wide range of distinct electrophysiological, neurochemical, and neuroanatomical conditions. Many factors in health, cognition, and life quality suffer from its absence and naturally occurring changes in sleep across lifespan could be linked to other age-related declines. The relationship between sleep and memory has been discovered and since then studied intensively, but due to the complexity inherent in both components, their relationship is even harder to grasp. A profound knowledge of the link between sleep and memory entails the potential to optimize reciprocal influence and thereby boost health, cognition, and well-being not only in younger, but also older adults. Therefore, having illustrated memory and sleep separately in the previous sections, the last part of the theoretical background will bring the relationship between sleep and memory into sharper focus in terms of basic research and practical application.

1.3. Memory and Sleep – Basic Research on Their Relationship

Disturbed sleep impairs memory (Drummond et al., 2000) and school performance (see Curcio, Ferrara, & De Gennaro, 2006 for a review). Closer considerations reveal that the effects of sleep on memory depend on the type of memory tested and on specific characteristics of sleep. The following paragraphs will illustrate the most important theories and paradigms concerning the relationship between sleep and memory. After outlining the importance of sleep for encoding and recall, the main focus will be on reporting investigations and theories about sleep and memory

consolidation and underlying mechanisms. At the end, findings on the nature of the relationship when obtained in an elderly population will be reported.

1.3.1. Sleep prepares the brain for encoding and recall

The longer the pre-sleep period of wakefulness and the higher the accompanying cerebral blood flow, the more sleep EEG activity slows down and becomes dominated by slow oscillation and delta activity (Clark et al., 1998; Horne, 1993). This SWA increase can even be locally detected in those cortical areas which were involved in prior learning tasks (Huber, Ghilardi, Massimini, & Tononi, 2004). In restoration sleep after 40 hours of sleep restriction, higher power density in low frequency bands (1-7 Hz) were recorded compared to normal nights of sleep. This increase was most prominent in frontal compared to parietal derivations, but disappeared across the sleep period (Cajochen, Foy, & Dijk, 1999; Finelli, Borbély, & Achermann, 2001). These results strongly suggest an accumulating need for recovery specifically in PFC during wakefulness ("prefrontal tiredness") and a restorative function of slow-waves, which diminish this need (Cajochen et al., 2006; Finelli et al., 2001). Therefore, SWA was suggested to represent an electrophysiological correlate of sleep need (Borbély, 1982), which is predominant in frontal compared to central and parietal areas (Finelli et al., 2001). The reason for the frontal dominance of slow oscillatory and delta activity is that the generation of slow waves is facilitated in PFC (Horne, 1993). From frontal origin, these slow-waves travel to posterior regions, extending to all neocortical parts (Massimini, Huber, Ferrarelli, Hill, & Tononi, 2004). Thereby, they prompt neuronal firing to be synchronized, generate spindles in the thalamus and sharp-wave ripples in the hippocampus (Achermann & Borbély, 1997; Steriade, 1999). Furthermore, they reduce levels of metabolism (Muzur, Pace-Schott, & Hobson, 2002). This is reflected in the negative correlation between delta band activity and prefrontal cerebral blood flow during sleep. Reduced metabolism possibly reflects an inhibited prefrontal area during prevalent delta activity (Hofle et al., 1997) or a sensory disengagement (Horne, 1993), although it must be noted that metabolic rate overall reduces during sleep. After sleep deprivation, brain metabolism is also significantly reduced in several brain areas including the PFC. After recovery sleep, metabolic rate increases in all these regions, although initial baseline levels are not achieved. It is worth noting that recovery in the frontal lobe is most pronounced, supporting the fact that sleep has a particularly important role for restoring PFC activity (Thomas et al., 2000; Wu et al., 2006). Together, the activity difference between sleep and wakefulness in PFC, the dependency of slow-wave power from previous wakefulness and the role of PFC for slow-wave generation hint at a restorative function of slow-waves for PFC, the seat of executive functions. In line with this conclusion, completely abolishing SWS by 36 hours of sleep deprivation leads to impaired performance on PFC associated

tasks compared to performance after a night of normal sleep (Harrison & Horne, 1998). Even a reduced level of slow-waves is enough to elicit negative effects on frontal brain activity and performance in PFC dependent tasks (Nilsson et al., 2005). Anderson and Horne (2003) recorded older adults' undisturbed night-time sleep at home and assessed several neuropsychological tests more or less sensitive to PFC function. For instance, they used a verbal fluency task to measure executive functioning. In this, subjects were asked to come up with words starting with a given initial letter or representing an item of a given category. The search through memory, which is required for managing the task, demands executive control. As patients with frontal as well as left hemispheric lesions show the most pronounced performance deterioration in such tasks (Miceli, Caltagirone, Gainotti, Masullo, & Silveri, 1981), they have proven to be sensitive to PFC function and are thus particularly suitable to test executive functions. As low EEG frequencies are most prevalent in the first NonREM episode and the risk of artefacts and disturbances is relatively small, the authors focused their analyses on delta activity in this period. They reported a correlation between the relative power in the low frequency band (0.5-1 Hz) in frontal derivations and waking performance in predominantly PFC dependent tasks after sleep. Delta power was however a negative function of age. This underlines the role of nocturnal EEG delta power for neuropsychological test performance in tasks associated with PFC function in old age (Anderson & Horne, 2003). In their review, Wilckens et al. (2012) also stated that memory retrieval might be inhibited by limitations in executive control, which result from an age-related PFC impairment. Consequently, they prompted future research to manipulate slow-wave sleep in healthy elderly and observe effects on memory performance to prove this model. According to the previous line of reasoning, older adults' performance in tasks associated with prefrontal functioning would indeed be expected to vary with sleep depth (Stavitsky, Neargarder, Bogdanova, McNamara, & Cronin-Golomb, 2012), although other aspects of cognition, like reaction times, vigilance, and alertness had proven resistant towards sleep deprivation (M. Adam, Rétey, Khatami, & Landolt, 2006; Duffy, Willson, Wang, & Czeisler, 2009). In summary, nocturnal slow oscillatory activity and memory performance are closely interlinked and it is possible that age-related performance deficits are related to decreases in delta activity, which make PFC restoration less efficient (Pace-Schott & Spencer, 2011). To investigate this possibility further, it was suggested to observe the effects of altered sleep depth on prefrontal function (Wilckens et al., 2012). The implementation of this proposal is an integral part of the third manuscript in this thesis.

Besides via executive control, deepened sleep might also improve other memory aspects. This can be assumed when taking into account the fact that the hippocampus also benefits from slow oscillatory activity. After one night of sleep deprivation, hippocampal activity during a declarative memory task presented the next day was significantly reduced. This deficit in activation is accompanied by performance decrements (Yoo, Hu, Gujar, Jolesz, & Walker, 2007). As total sleep

deprivation was however less ecologically valid than intact but shallow sleep, Van der Werf et al. (2009) acoustically disrupted the sleep of elderly women to achieve experimentally induced shallow sleep, poor in slow (SWA) and rich in fast (alpha) frequencies. Following normal versus disturbed sleep in a within-subjects design, subjects were confronted with a memory encoding task the next day, performed in a magnetic resonance imaging (MRI) scanner. Encoding after induced SWA reduction was accompanied by selective activation reductions in parts of the hippocampus. These reductions in brain activation were reflected in a lower encoding performance after disturbed as compared to normal sleep. This was only true for the explicit, but not the hippocampus-independent, implicit memory task. These results show that also intact, but shallow sleep negatively influences hippocampal activation during next day encoding, lowering performance (Van Der Werf et al., 2009). These results tally with those attained by Antonenko et al. (2013). Applying transcranial slow oscillation stimulation (tSOS) of 0.75 Hz in frontal sites during sleep enhanced SWS, SWA, and the encoding of a hippocampal dependent declarative task, thus prepared the brain for the acquisition of new incoming information.

To sum up, studies show that the hippocampus and prefrontal cortex are sensitive to sleep, especially deep sleep, which prepares and optimizes the brain for upcoming encoding situations and recall. Having established the critical involvement of both, the hippocampus and the prefrontal cortex in memory processes, their functional dependency on slow oscillatory activity emphasizes the critical role of sleep for optimal learning and memory recall. Its role for memory consolidation will be outlined next.

1.3.2. Sleep benefits the consolidation of memories

The previous paragraphs have impressively demonstrated the importance of deep sleep for encoding and recall, particularly for prefrontal and hippocampal dependent, explicit memories. Sleep is however also highly important for optimum consolidation of memories. Meanwhile, several assumptions about the mechanism underlying this supportive role have been developed, discussed and fed with evidence. The following paragraphs will give a short overview of the most important theories and the current state of scientific knowledge.

Sleep – passive shelter or active factor?

Investigating the nature of forgetting it was discovered that during a retention period including sleep, forgetting was reduced compared to an episode containing wakefulness (Ebbinghaus, 1992). This observation was confirmed in a series of systematic studies (Benson & Feinberg, 1975; Jenkins & Dallenbach, 1924; van Ormer, 1932) and interpreted as the result of the

absence of interference during sleep, which had impaired the wake group's performance. The more detailed the investigations became the more they uncovered inconsistencies sufficient to rattle the theory of sleep as a passive shelter. Benson and Feinberg (1977) demonstrated superior memory performance when sleep instead of wakefulness directly followed learning. This advantage even persisted after 24 hours when both groups had passed equal amounts of both brain states. The passive interference theory was not sufficient to explain this time dependency of the sleep effect. Further, qualitative changes in memory that were reported across sleep could also not be explained by a mere shelter (Fischer, Drosopoulos, Tsen, & Born, 2006; Wagner, Gais, Haider, Verleger, & Born, 2004). The first study to undeniably dispute the conclusion of a passive shelter was done by Ellenbogen et al. (2009). They based their paradigm on the assumption that if sleep only represents a respite for new memories, interference after sleep should distort memories more than when intermediate sleep helped consolidation. Therefore, the authors challenged memory stability after sleep by presenting interfering material right before recall. Results demonstrated that this interference optimally revealed the benefits of sleep by pronouncing the difference in recall performance after sleep versus wake. This pattern indicated that during sleep, memory was not only passively protected from interference, but was actively strengthened in a way that made it less susceptible to interference. After wakefulness, on the contrary, the memory trace remained highly damageable. Not testing the stability after sleep by an interference task had underestimated the effect of sleep on memory so far. Only the refined behavioral paradigm unmasked the size, the stabilizing effect sleep has on memory and discerned its active role in memory consolidation. The search for the property unique to sleep but crucial for memory stability abounds.

All in all, adequate paradigms were able to rule out the hypothesis that sleep benefits memories as a passive shelter from interference. Studies instead demonstrated its active involvement in increasing resistance to disruptive new encoding, but the causal mechanism remained elusive. Theories are presented in the following.

What in sleep is it that benefits memory? – dual process and sequential hypothesis.

More finely-tuned studies showed that certain sleep stages provide more or less advantageous conditions for the consolidation of specific forms of memories (for revs see e.g., Fishbein & Gutwein, 1977; McGrath & Cohen, 1978). Animal studies quite consistently reported memory benefits from REM sleep in diverse study designs (Fishbein, Kastaniotis, & Chattman, 1974; Hennevin, Leconte, & Bloch, 1974; Smith, 1985; Wetzel, Wagner, & Balschun, 2003). Memory was however mostly measured with fear or shock avoidance tasks, representing emotional and procedural learning, disregarding declarative memories. In humans, results concerning the contribution of specific sleep stages to memory were inconsistent (e.g., Barrett & Ekstrand, 1972;

Chernik, 1972; Ekstrand, Sullivan, Parker, & West, 1971; Lewin & Glaubman, 1975), especially for declarative memories (Castaldo, Krynicki, & Goldstein, 1974). Plihal and Born's (1997) eminent study included both memory systems in a single study design, based on the so called night half paradigm (Fowler, Sullivan, & Ekstrand, Bruce, 1973; Yaroush, Sullivan, & Ekstrand, 1971) which takes advantage of the fact that early sleep is dominated by NonREM sleep while REM sleep is more prevalent in the second night half. Advantageously, lighter sleep stages 1 and 2 are equally distributed in first and second night half. Thus, comparing memory performances after retention intervals including the first versus the second half of the night enables inferences on the separate contributions of the respectively dominant sleep stage. Results showed that, for declarative memory, the first half of the night was more advantageous than the second half. This was reversed for procedural performance which benefited more during late sleep. These findings deliver considerable support to the dual process hypothesis which claims that REM and NonREM sleep act differently on the diverse memory systems. More precisely, SWS benefits declarative memory whereas REM sleep facilitates consolidation of procedural memory (Plihal & Born, 1997; Smith, 1995). Although it still persists tenaciously, this strict separation could not always be confirmed and in some studies REM sleep benefited episodic memory (Fogel, Smith, & Cote, 2007; Rauchs et al., 2004) just as SWS proved crucial for procedural memory (Gais, Plihal, Wagner, & Born, 2000; Huber et al., 2004). As mentioned earlier, the memory systems are neither theoretically nor practically clear-cut and separable (Peigneux, Laureys, Delbeuck, et al., 2001; Tulving, 1993). This inconclusiveness brings with it a blurring of memory systems hard to disentangle in task construction. As a consequence, some tasks might entail contributions of both memory systems and are not system-pure (Born & Wagner, 2004; Peigneux, Laureys, Delbeuck, et al., 2001; Poldrack & Rodriguez, 2004). This could have led to inconsistent results concerning the role of sleep for memory. Apart from that, the divergent findings could also reflect that SWS and REM sleep must sequentially be passed through to complementarily achieve fully stabilized memories. This is what the sequential hypothesis assumes (Gais et al., 2000; Giuditta et al., 1995).

Together, the unclear pattern of results suggests that even sleep stage levels might not be enough to understand the finely entangled links. A closer consideration of underlying neurobiological parameters and brain oscillations occurring during sleep seems to be required for greater understanding, as offered next.

Spontaneous memory reactivations and the memory transfer.

Some years back, cell populations in hippocampal formation were discovered that code for particular locations in a place and increase firing rate when the animal returns to this position (O'Keefe & Dostrovsky, 1971). These place specific cells maintain common increased firing over

weeks to months (Thompson & Best, 1990), but reach highest firing rates during sleep. This observation gave rise to the interpretation that this "replay" is the reflection of memory processing, obviously emphasized during sleep. Following up on this assumption, Pavlides and Winson (1989) investigated the firing characteristics of these hippocampal place cells during wake and sleep. They discovered that cell activity during learning influenced characteristics of the activity during sleep. Later, Wilson and McNaughton (1994) reported that in rats, neuronal ensembles in the hippocampus which were active during learning were similarly reactivated during following sleep. These spontaneously appearing reactivations (Kudrimoti, Barnes, & McNaughton, 1999) occurred in the same order as during experience (Skaggs & McNaughton, 1996), although faster (Euston, Tatsuno, & McNaughton, 2007). Besides the hippocampus, these reactivations also extended to neocortical circuits during sleep (Qin, McNaughton, Skaggs, & Barnes, 1997). It is assumed that this co-occurring reactivation in the hippocampus and the neocortex reflects memory consolidation during which newly formed memories in the hippocampus are transferred to neocortical areas for long-term storage (Buzsaki, 1996, 1998; Frankland & Bontempi, 2005; Ji & Wilson, 2007; McClelland et al., 1995). Studies showing a sleep-dependent shift from hippocampal to neocortical activation during recall over time provide evidence for the conclusion that memory is integrated into neocortical sites for permanent storage during sleep (Gais et al., 2007). The notion that the neuronal reactivations cause memory consolidation is the core of the active system consolidation hypothesis. The cell reactivations were shown to be associated with certain sleep parameters (Buzsaki, Horváth, Urioste, Hetke, & Wise, 1992) and mainly apparent during SWS (Born, Rasch, & Gais, 2006; Kudrimoti et al., 1999; Peigneux et al., 2004; M. Wilson & McNaughton, 1994). The predominance of reactivations during SWS results from SWS specific electrophysiological events, which elicit them (Ji & Wilson, 2007): Neocortical slow oscillations during SWS prompt and coordinate the appearance of hippocampal sharp-wave ripple events (Buzsaki, 1998) and thalamo-cortical spindle activity (Steriade, 1999). The interplay between all three events enables the effective transfer of new information from the hippocampus to neocortical regions (Sirota, Csicsvari, Buhl, & Buzsáki, 2003). Evidence for the involvement of reactivations during SWS in memory consolidation comes from studies reporting correlations between the amount of neuronal activity during sleep and performance improvements (e.g., Peigneux et al., 2004). The causal involvement of slow oscillatory activity in memory formation was shown in a study which experimentally induced slow oscillations of 0.75 Hz frequencies with transcranial direct current stimulation (tDCS) during SWS. This deepened sleep and facilitated retention of declarative memory (Marshall, Mölle, Hallschmid, & Born, 2004). Besides physiological parameters, specific in SWS, neuromodulatory conditions favor spontaneous hippocampal reactivations and hence, information transfer. First, levels of acetylcholine act as a switch between encoding and consolidation mode. While SWS specific low acetylcholine levels offer a

neurotransmitter milieu beneficial for initiating plastic changes in neocortical brain areas, high cholinergic tone completely blocks memory consolidation and rather benefits encoding (Gais & Born, 2004; Hasselmo & Giocomo, 2006; Rasch, Born, & Gais, 2006). Second, as high amounts of cortisol impair hippocampal long-term potentiation (LTP), low levels of cortisol which prevail during SWS actively contribute to the formation of hippocampus-dependent memories (Korz & Frey, 2003; Plihal & Born, 1999).

In short, physiological events and biological characteristics specific for SWS promote and initiate the hippocampal-neocortical dialogue during SWS. This communication reflects the transfer of memories from hippocampus into neocortical networks and is expressed by spontaneous reactivations of brain areas involved in learning (Born et al., 2006; Oudiette & Paller, 2013). These features corroborate a causal relationship between SWS and memory consolidation. It must however be noted that some studies only focused on SWS and did not even consider investigating other sleep stages. Although most of the reactivations were recorded during SWS (Buzsaki et al., 1992; Ji & Wilson, 2007; Kudrimoti et al., 1999; M. Wilson & McNaughton, 1994), they also appeared during REM sleep (Louie & Wilson, 2001; Pavlides & Winson, 1989; Poe, Nitz, McNaughton, & Barnes, 2000) and wakefulness (Carr, Jadhav, & Frank, 2011; Karlsson & Frank, 2009; Peigneux et al., 2006).

Not only did replay occur during REM sleep, but it even occurred after 24 hours (Louie & Wilson, 2001), while reactivations in SWS were only seen shortly after learning (Pavlides & Winson, 1989; M. Wilson & McNaughton, 1994). It was speculated that replay during SWS is just a continuation of the activation initiated during learning while activity in REM after 24 hours is “true” reactivation (Stickgold et al., 2001) and evidence from animal studies led the researchers to conclude that they also contribute to memory processing (Hennevin, Hars, Maho, & Bloch, 1995; Ribeiro et al., 2002). However, in animals as in humans, increased activation in task-related brain areas in REM sleep after learning compared to non-trained subjects was only demonstrated for non-declarative, implicit memory tasks (Maquet et al., 2000; Peigneux et al., 2003). Thus, in line with the dual process hypothesis, reactivations of declarative tasks were shown during SWS and replay of implicit or procedural tasks were detected during REM sleep. The role of REM sleep for declarative memory was subjected only in theory. The active system consolidation hypothesis suggests that REM sleep stabilizes declarative memories in a second step after their reorganization during SWS (Diekelmann & Born, 2010; Rasch & Born, 2013). This theoretical assumption has however not yet been confirmed by findings indicating more stable declarative memories after REM sleep. So far, only the molecular and electrophysiological characteristics of REM sleep which might benefit long-term potentiation corroborate the theory, such as elevated expression of immediate early genes, known to be involved in plasticity (Ribeiro et al., 2002) and the high cholinergic tone which enables the activity of those plasticity-related genes (von der Kammer et al., 1998). Additionally, in rats, REM sleep specific ponto-

geniculo-occipital (PGO) waves and theta rhythms (4-8Hz) dominating REM sleep have proven relevant for memory consolidation (Datta, 2000; Louie & Wilson, 2001; Poe et al., 2000). Not only did PGO wave density change after avoidance training, but this change also paralleled the increase in task performance (Datta, 2000). Theta activity correlates with PGO waves, is known to induce long-term potentiation (LTP) (Maquet, 2001; Pavlides, Greenstein, Grudman, & Winson, 1988) and was suggested to pace memory storage and reactivation (Louie & Wilson, 2001). Together, reactivations appear in SWS and REM, but these sleep stages seem to contribute differently to memory consolidation, not least depending on the memory system engaged (Hennevin, Huetz, & Edeline, 2007). Whether replay during REM sleep reflects stabilization of declarative memories after the transfer that happened in SWS has not been proven yet, but will be considered in manuscript 1.

In summary, these studies demonstrate the existence of memory reactivations during wake as well as during NonREM and REM sleep. To establish their behavioral relevance, correlations between physiological processes and behavioral performance were investigated. The active system consolidation hypothesis offers a theoretical framework for those results by combining several well-documented accounts: the dual-process account, the sequential hypothesis, and the standard two stage model of memory (Krakauer & Shadmehr, 2006). Thereby, it goes beyond the sleep stage level and incorporates specific physiological and biological characteristics occurring during sleep. However, the assumed stabilizing role of REM sleep is not confirmed so far. Further, reported correlations do not imply a causal involvement of reactivated neuronal populations in memory consolidation (Hennevin et al., 2007). To draw conclusions on the behavioral significance of reactivations, the consequences of their manipulation must be considered. Research on that has successfully been done as reported in the upcoming passages.

Induced memory reactivations and their behavioral consequences.

If spontaneous reactivations played a causal role for memory performance, a selective increase of replay should specifically strengthen reactivated memories. Comparing recall performance of memories for which replay was boosted with those that were not additionally reactivated, enables inferences on their behavioral significance. A possibility to manipulate reactivations during sleep was tested first by Hars et al. (1985). To directly stimulate the memory trace, the non-awakening mild ear shock, which repeatedly preceded a stronger foot shock during learning, was delivered again during REM sleep or during wake. Confrontation with a part of the learning stimuli during sleep was intended to act as a cue, inducing associations with the learning situation. Behavioral data showed enlarged conditioning effects when the cue had been presented during REM sleep and when memories were fresh. Conditioning was lessened when ear shocks were presented during wake or SWS as a later study showed (Hars & Hennevin, 1987). Another study

revealed increased activation in hippocampal neuronal populations during learning and also later during REM sleep, elicited by a tone that had been paired with a foot shock. This parallel activation was assumed to reflect "recognition" of behaviorally relevant stimuli during sleep (Maho, Hennevin, Hars, & Poincheval, 1991). In a nutshell, cueing of memories during REM sleep is possible and influences behavior and brain activity. Of note, again, avoidance conditioning tasks, thus emotional learning, were used in these animal studies. Translating this paradigm into human work led to heterogeneous results. While auditory stimuli presented during Morse code learning increased retention when redelivered during REM sleep (Guerrien, Dujardin, Mandal, Sockeel, & Leconte, 1989), learning-associated odor cues during REM sleep did neither affect declarative nor procedural memory performance in humans (Rasch, Büchel, Gais, & Born, 2007). Also when cueing took place during wakefulness instead of REM sleep, memory performance was not affected. In contrast, when the odor was re-exposed during post-learning SWS, declarative memory was improved. On a neuronal level, fMRI analyses demonstrated increased activation in hippocampus during odor cueing, most pronounced during SWS (Rasch et al., 2007). A later study found effects of an odor cue given during SWS also in EEG delta activity (1.5-4.5 Hz) and spindles (13-15 Hz) which accompanied the memory benefit. The power increase in these frequency bands suggested a facilitation of synaptic plastic processes involved in the observed memory enhancement (Rihm, Diekelmann, Born, & Rasch, 2014). Studies in which sounds acted as cues could even specifically reactivate only certain items and compare their retention with un-cued ones within one subject and sleep period. Indeed, performance for reactivated stimuli was improved compared to un-cued items (Rudoy, Voss, Westerberg, & Paller, 2009). This finding demonstrated the specificity of the beneficial effect.

Together, findings showed that if cues act as a trigger and reactivate the learning context during sleep, outcomes differ depending on brain state and memory system. Declarative, but not procedural memories were boosted after reactivation during SWS, but neither during REM sleep nor wakefulness. This supports the assumption that also spontaneously occurring reactivations during SWS benefit memory consolidation and underlie the observed sleep effect. Still, the reason for the improvement is unclear. According to the active consolidation theory, it results from the memory transfer during SWS. However, theoretically, transferred memories are labile and need to be stabilized during ensuing REM sleep (Nader & Hardt, 2009; Nader, Schafe, & Le Doux, 2000). As performance enhancements can however also be observed after the presentation of an acoustic cue during SWS in a 90 minute nap, in which minimal amounts of REM sleep appeared (Antony, Gobel, O'Hare, Reber, & Paller, 2012), the contribution of REM sleep to stabilization is questionable. Either the reorganization during SWS is sufficient to improve memory performance, or memories are already stabilized in SWS, before REM sleep. To follow up on the question in which stage memories

are stabilized, a more refined paradigm was implemented to effectively test memory stability, along the lines of Ellenbogen et al. (2009).

Testing memory stability after induced reactivation.

In a within-study design, participants learned a visuospatial task in the presence of an odor. Subjects were either re-exposed to the odor or an odorless vehicle during SWS after learning. Subjects were awakened before the first REM sleep cycle and learned an interfering task without olfactory stimulation in order to challenge memory stabilization. The original task was recalled 30 minutes later. Interference learning impaired memory for the original task more strongly when memories were not reactivated during SWS. Becoming less prone to interference through cueing during SWS hints at a strengthening, stabilizing role of reactivations during SWS (Diekelmann, Büchel, Born, & Rasch, 2011). To compare results, the same design was applied to a wake control group. Here, effects were opposite and performance was significantly more impaired after cueing during wakefulness than after the retention interval without cueing. This favors the conclusion that reactivation during wakefulness indeed destabilizes memories, but strengthens memories when applied during SWS. Possibly, reactivations during sleep serve the reorganization and stabilization as encoding is suppressed. In contrast, during wakefulness, memories are weakened after renewed reactivation, because encoding in a new context takes place. Cueing-associated brain activation supports this assumption. fMRI analyses show active hippocampal and neocortical regions during cueing in SWS, which are associated with the transfer of memories to long-term storage (Gais et al., 2007). Contrary to this, during wakefulness, PFC is activated, which is associated with working memory activity, for instance during comparison of stored memories with new ones (Diekelmann et al., 2011). Thus, inducing reactivations has revealed differential functions of neuronal replay depending on the brain state during which it occurs. Thus, this design proved appropriate for investigating the role of REM sleep reactivations for memory stability. Although active consolidation theory states that REM sleep stabilizes the memory trace after redistribution during SWS, reactivations during SWS were apparently sufficient to increase resistance to interference (Diekelmann et al., 2011). It is possible that reactivations also stabilize memories when co-occurring with SWS specific events like spindles or slow oscillations. On the other hand, stabilization might only be initiated, but not accomplished during SWS and is more pronounced during ensuing REM sleep. This uncertainty forms the basis of the first manuscript in which the function of reactivations observed during REM sleep for stability of declarative memories is investigated in order to bridge this research gap.

Together, results demonstrate a brain state dependency of declarative memory reactivations: While reactivating memories during SWS initiates stabilization, destabilization follows

when cueing is administered during wakefulness. This favors the assumption that the beneficial role of sleep for memory is based on spontaneous memory reactivations which enable a transfer of memories into long-term storage and integration into existing knowledge, which stabilizes these memory traces. However, the role of reactivations during REM sleep remains questionable. As most of the studies these theories were based on tested younger adults, it is not clear whether they also hold for older adults. Thus, the relationship between sleep and memory in older age will be outlined next.

1.3.3. Relationship between sleep and memory in advanced age

Declines in SWS and SWA that appear across the lifespan parallel loss of memory performance (Backhaus et al., 2007; Mander et al., 2013; Ohayon et al., 2004) and accompany mild cognitive impairment (Westerberg et al., 2012). This could reflect the fact that the relation between sleep and memory persists into old age and leads to a reciprocal negative influence. However, it is also possible that a reduced effectiveness of sleep for memory consolidation accounts for the losses in memory. Data on the relationship between sleep and memory across age is controversial. One study tested visuospatial memory before and after a period of sleep versus wake in younger and older adults and reported age-related differences in the sleep effect. While the forgetting rate was reduced across sleep compared to wakefulness in the younger sample, sleep did not prevent memory from reductions across sleep in older adults. Neither age-related differences in SWS nor an association between SWS and forgetting rate was found. Thus, older adults seem to have had a particularly good sleep, which still did not support memory consolidation. These results favor the conclusion that the benefit of sleep for memory reduces with age (Cherdieu, Reynaud, Uhlrich, Versace, & Mazza, 2014). Scullin (2013) investigated sleep-dependent memory consolidation of verbal memory in younger and older adults. He reported reduced SWS amounts and memory retention benefits from sleep in older compared to younger adults. He also failed to find a positive correlation between SWS amount and word pair retention in the older sample which was present in younger adults. Thus, both data sets suggest that the sleep-memory relationship prevalent in younger adults might not be maintained in older adults. Based on such data, researchers assume that besides SWS and memory performance, their relationship could also weaken with age (Hornung, Danker-Hopfe, & Heuser, 2005; Pace-Schott & Spencer, 2011). This would imply that declarative memory performance is not improved even after SWS enriched sleep in older adults. However, a very different pattern appeared in a study conducted by Backhaus et al. (2007). They reported lower amounts of word pair retention across sleep in middle-aged compared to younger subjects. This was however only true for the first, SWS-rich sleep phase, but not for the late, REM sleep–rich period.

Reductions in early sleep memory benefit in middle-aged were accompanied by reduced SWS amounts compared to the student sample, hinting at its importance for the benefit. When comparing sleep periods containing similar amounts of SWS (i.e., early sleep in older and late sleep in younger adults), age-related differences in memory retention were absent. These results indicated an association between memory retention and SWS amounts as well as age, but suggested a more critical involvement of SWS amounts compared to age. Mander et al. (2013) also reported a degree of memory retention which depends on the amount of nocturnal prefrontal as well as global SWA in elderly subjects. Furthermore, both measures (global SWA and memory retention) were correlated with prefrontal gray matter density, suggesting that reduced memory consolidation in advanced age partly depends on PFC gray matter atrophy, which lowers power in SWA. Based on these findings they established a framework in which age-related PFC atrophy predicts the degree of SWA disruption, which reduces memory consolidation in older adults (see Figure 2).

Figure 2. Model of the Relationship between PFC, SWA, and Memory Consolidation

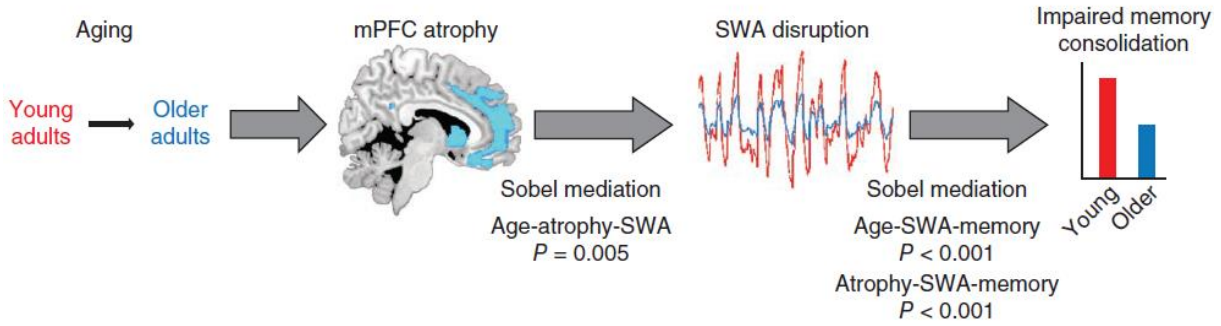


Figure 2. adapted from Mander et al. (2013). The model displays the mediation findings of Mander et al. (2013). Gray matter atrophy, associated with aging, mediates SWA disruption. It is suggested that this interplay in turn influences the degree of memory retention.

The latter two studies thus demonstrate that although SWS, SWA, and memory performance decline across age, the functional relationship between both components persists. Additionally, two other studies reported spared memory consolidation across sleep in a word pair learning task (J. K. Wilson, Baran, Pace-Schott, Ivry, & Spencer, 2012) and in episodic recall in older adults (Aly & Moscovitch, 2010). Sleep conferred benefit to memory in both age groups to the same extent. Critically, for both studies no polysomnographic sleep parameters were available. Nevertheless, these contradicting results defy mere inference from age-related changes in sleep physiology that its relevance for memory consolidation changes, based on knowledge derived from studies investigating younger adults. Effects of manipulated sleep depth on memory retention across sleep could give an

interesting hint at the nature of their relationship in older age. This will be one issue of the third manuscript.

Age effects in memory reactivations have hardly been studied up to now. One study in rats recorded neuronal activity during track running and a subsequent rest period and compared it between younger and older rats. The hippocampal replay, young rats exhibited in the short rest periods, was not reliably preserved in older animals. In the older rats, the temporal sequence of the activity pattern during track running and rest was disorganized. Critically, the temporal accordance between neuronal activation during learning and rest was correlated with the degree of spatial memory (Gerrard, Burke, McNaughton, & Barnes, 2008). Thus, this study hinted at neuronally-based alterations in the relationship between sleep and memory across lifespan. However, further studies are required to follow up on this hypothesis.

All in all, although impaired memory consolidation as a consequence of SWS reductions would be logically expected, this pattern is not consistently found. Some authors have concluded that the strength of the relationship between sleep and memory also declines across lifespan, while others assume a deteriorating reciprocal influence. However, age-related changes in the relationship between sleep and memory are still understudied and need further consideration before established conclusions can be drawn. The third manuscript will contribute more evidence.

1.3.4. Interim summary

In summary, sleep promotes learning and recall and actively contributes to memory consolidation. Spontaneously occurring reactivations of cortical areas previously engaged during learning seem to reflect an offline memory processing which is responsible for the memory improvement obtainable after a sleep period. It was shown that external initiation of reactivations by cueing is possible and has consequences for brain activity and behavior. Studies manipulating reactivations by cueing demonstrated their brain state dependency: reactivations stabilize memory traces when they appear during SWS, but return them into a labile state, prone to interference when occurring during wakefulness. The open question, the first manuscript will answer, concerns the function of REM sleep related reactivations for the stability of declarative memory. Whether the relationship between sleep and memory persists across lifespan cannot conclusively be derived from current research as those very few studies including older adults that exist reveal inconsistent results, and extrapolation from data collected in younger adults to the functionality of mechanisms in advanced age is not valid. More comparative studies including a sample of younger and older adults are required.

1.4. Memory and Sleep – A Practical Application of Their Relationship

From a practical perspective, the relationship between sleep and memory implies that sleep might be a target for the improvement of cognitive performance (Pace-Schott & Spencer, 2011; Wilckens et al., 2012). If spontaneous SWS reactivations are vital for memory consolidation, it should be possible to support memory consolidation by increasing the time spent in SWS so that more spontaneous reactivations can appear. What favors this consideration is that childhood is not only characterized by a greater amount of brain plasticity (Brehmer et al., 2007), but also by higher amounts of SWS than adulthood (Ohayon et al., 2004). Presumably, this enlarged amount of SWS is crucially involved in brain maturation by offering enough opportunities for reactivations to occur to stabilize all the new memory traces. On an interpersonal level it must be noted that very often correlations between memory benefits and SWS amounts are not found (Castaldo et al., 1974; Lahl, Wispel, Willigens, & Pietrowsky, 2008). Thus, it cannot be concluded that subjects with more SWS generally have a better memory due to improved memory consolidation. However, on an individual level, positive memory enhancements were shown to correlate with SWS amounts so that within one person, the extent of memory enhancement varies with the amount of SWS per night (Backhaus et al., 2007; Tucker et al., 2006). Therefore, manuscripts II and III will test hypnotic suggestions as a method to increase the amount of SWS and observe possible behavioral consequences for declarative memory. Thus, the relationship between sleep and memory will be presented from another angle in the following sections, namely the opportunity to practically apply it in everyday life. First, successes of hypnotherapy for the treatment of sleep problems will provide a first impression of its effectiveness in influencing sleep. To better understand the phenomenon, diverse terms will be introduced and explained in the middle part of this section. Finally, although some studies have provided objective evidence for hypnosis, gaps regarding objective indications of its power to influence sleep still exist. These will be discussed as a last point, also in respect of the results' transferability to an older sample.

1.4.1. Hypnotherapy in patients with sleep disturbances

An overwhelming amount of people suffering from sleep problems presents challenges to society by increasingly engaging the services of health professionals (Bixler et al., 1979). As pharmacotherapy is the most widely recommended and used intervention for insomnia (Morin et al., 1999), consumption of sedative medication is extended (Weyerer & Dilling, 1991). However, drug intervention is accompanied by aversive side effects, has limited therapeutic effect and is thus not an

adequate long-term treatment (Hohagen et al., 1993). Therefore, psychological and behavioral interventions should be chosen for treating insomnia (Pallesen et al., 1998). Among non-pharmacological treatments, hypnosis represents a promising approach to positively influence sleep and is considered free of risk (Deivanayagi, Manivannan, & Fernandez, 2007). A clinical study compared the efficacy of an insomnia therapy including hypnosis with a progressive relaxation, self-relaxation and a no-treatment control group. All treatments reduced the number of awakenings per night and boosted feelings of being rested in the morning. Additionally, the progressive and hypnotic relaxation resulted in a reduced time to fall asleep. This demonstrated the effectiveness of the hypnotic relaxation method to achieve sleep improvements (Borkovec & Fowles, 1972). A later study confirmed the positive effect of hypnotic relaxation on sleep onset latency (Stanton, 1989). Symptom reductions or eliminations of sleep problems after one or two sessions of hypnotherapy were maintained even after a 5 year follow-up retest (Hauri, Silber, & Boeve, 2007). Stanton (1999) presented case reports about three patients suffering from sleep disturbances. Difficulties falling asleep, awakenings during the night, and problems in adapting the sleep times to a shift-work schedule could successfully be treated and symptoms were reduced enduringly. These cases impressively underlined the effectiveness of treating sleep problems with hypnotic relaxation or imagination and stressed how easily and widely the technique can be applied. In the second and third manuscript, the influence of hypnosis on sleep and in second place the impact of this change on memory is tested. As these studies revolve around a phenomenon neither easy to define nor explain (Bongartz, Flammer, & Schwonke, 2002) and which is subject to much controversy and skepticism, it is inevitable that a selection from the plethora of definitions that exist is presented, in an attempt to make sense of what is inherent in this exceptional state first.

1.4.2. Definition of hypnosis, induction, suggestion and suggestibility

The origin of the word hypnosis is “hypnos”, the Greek word for sleep (Halsband, 2012). Braid (1845), a medical doctor, coined the term referring to a neurological phenomenon of partial sleep which he and his colleagues had observed. In his view, the analgesic effect hypnosis could elicit resulted from a temporal shutdown of the sensory system after overstraining nerves through the fixation of a single stimulus. Medical substrates later replaced hypnosis as analgesic method whereby it temporarily lost its significance for medicine. Later therapists stressed the hypnotists’ authority as the basis for the effectiveness of hypnosis, attributing a heteronomous character to hypnosis, partly still prevailing today (Revenstorf, 2009). This psychologically based reasoning was shared by the so called non-trance theorists. In their view, stances of social psychology, like compliance elicited by pressure on behalf of the hypnotist or role-taking were assumed to underlie suggestive behavior and

were worthy to be called hypnosis (Barber & Calverley, 1965). Contrary, trance theory regarded hypnosis as a separate state of consciousness in which suggestions are most powerful (Hilgard, 1973). As hypnotic phenomena, although weaker, also occurred without previous induction of a hypnotic state, proponents of the non-trance theory saw no need to establish a special state. This disarray in definition mainly arose as research was faced with the difficulty of finding physiological indicators of a modulated brain activity. Non-state theorists concluded that no such state exists while state theorists argued that also sleep was not measureable before the invention of the electroencephalogram, while no-one would have doubted its existence (Hilgard, 1973). The socio-biological model accepted in today's definitions still reflects these discrepancies and the attempts to unite both the trance theory and the non-trance theory (Lynn & Rhue, 1991). In his definition, Revenstorf (2009) focuses on the role of hypnosis as a procedure used to externally initiate a state of changed consciousness, referred to as trance. Thus, hypnosis represents the method used to elicit the trance state in which usual behavior patterns are altered, mainly by verbal stimulation. During hypnosis, perception and cognition are altered, subjects experience a different emotionality, and attention is wider or narrower than usual (Revenstorf, 2005). Kihlstrom (1987, 2013) describes hypnosis as a social interaction between a subject or patient and the hypnotist in which imaginative experiences are offered by the hypnotist and responded to by the subject. Halsband (2012) adds a neurobiological point of view to this definition and describes hypnosis as a different state of consciousness, which is hallmarked by a change in brain activity accompanied by reduced critical thinking and sharpened and increased degree of compliance, imagination abilities, mental relaxation, and attentional processes (Hinterberger, Schoner, & Halsband, 2011). Oakley and Halligan (2009) also base their definition of hypnosis on EEG and fMRI studies reporting alterations in brain activation and functional connectivity suggesting the existence of a distinct hypnotic state. They define hypnosis as a state of changed mental activity, which can be elicited by an induction procedure. In this altered mental state, an increase in absorption and attention accompanies a reduction in distractibility. Together, hypnosis is sometimes referred to as the altered mental state, but might also describe the method or interaction between patient and hypnotist. As generally the notion of the trance theory is more common, and as recent neuroscientific evidence for differences between wake and hypnosis in terms of brain activation and electrophysiology exist (e.g., Kosslyn, 2000), the modified state of consciousness will be referred to as hypnosis in this thesis, based on Oakley and Halligan's (2009) definition. To reach the altered state in which behavior can be influenced, an induction technique is applied.

The induction procedure

There is a set of conventional procedures to initiate hypnosis: Subjects are exposed to instructions directing attention towards the hypnotist´s words. Often, the focus is shifted from external to internal processes while eyes are fixed on a stimulus. Thereby, perceptions are described involving all sensations and external circumstances, like warmth of body parts, heart rate, respiration, or sounds coming from outside. Attention is then shifted towards internal mental processes and the creation of an imagined reality (Revenstorf, 2010). To provide time for this switch, steps on a stair or stages on a journey can be used to represent a step-by-step deepening of the hypnotic state and increased relaxation (Hinterberger et al., 2011). The voice of the hypnotist is calm, fairly monotonous and soft (Hilgard, 1973).

Suggestions

When the hypnotic state is entered, verbal instructions can be given to elicit changes in perception, experience, behavior, actions, affect, or cognition (Terhune & Kadosh, 2012). These are also referred to as suggestions. Suggestions can be formulated in different manners. Classical hypnosis was characterized by direct and strict announcements, clearly formulating orders given to the subjects (Bongartz et al., 2002). These are referred to as direct suggestions. In contrast, Milton Erickson founded modern hypnosis and emphasized that static value systems and critical rationality can counteract therapeutical interventions. Therefore, he developed a number of techniques helping to overcome these self-made borders. Indirectly given suggestions are one important example. They are rather understood as real “suggestions”, i.e. possibilities the patient might or might not adopt. This is underlined by spreading auxiliaries (“you can”, “you need not”) or words like “maybe” “possibly”, or “if you’d like to“ (Revenstorf, 2010). Contrary to direct orders, they do not require conscious processing. This enables circumvention of rationality and value and avoids resistance. One technique of indirect suggestions considered very important in Ericksons’ tradition is the use of metaphors. Metaphors enable an indirect transport of knowledge from one to another situation while leaving space for interpretation and fantasy. This opens up a wide field for the generation of solutions instead of provoking restrictions by trying to give fixed advice (Revenstorf, Freund, & Trenkle, 2009). Metaphors can either be fairy tales, stories, anecdotes, or even jokes or riddles. They deliver information more easily and understandably and have the power to also visualize body related processes. For instance, blood circuit can be symbolized by a river. By creating a story about this river, blood circuitry can be influenced. Due to this simplification, this method can be applied with a wide range of patients or subjects and does not require a certain skill or level of intelligence (Revenstorf et al., 2009). Statements or instructions can also be given for a behavior supposed to be

enacted after leaving the hypnotic state, called posthypnotic suggestions. For example, posthypnotic amnesia suggests a lack of memory for what had happened during the hypnosis or for any particular suggestion. Despite a clear-cut separation, the terms hypnosis and suggestion are often mixed up (Halligan & Oakley, 2013). Suggestions describe given statements to influence behavior while hypnosis refers to the altered mental state. Suggestions can in fact also be successfully given without previous induction of hypnosis (Hilgard, 1973). Still, and importantly, responsiveness to suggestions is fostered when applied after hypnotic induction (Halligan & Oakley, 2013; Oakley & Halligan, 2009). In general it is even inferred that hypnosis was induced successfully when responses to suggestions appear (Green, Barabasz, Barrett, & Montgomery, 2005). The ease of inducing hypnosis does not only depend on the success of the induction, but also on traits of the subject, particularly his suggestibility, as described in the following section.

Suggestibility

Suggestibility describes the degree of responsiveness to hypnotic procedures that subjects can experience. Due to the high retest-reliability over 25 years it is regarded as a trait, although certain interactions between person and situation must be considered (Piccione, Hilgard, & Zimbardo, 1989). Standard self-rating scales were developed, which measure the construct and allow for classifications into high, medium and low suggestibility. The scale we used in our studies is the Harvard Group Scale of Hypnotic Suggestibility, translated into German by Walter Bongartz (1985) and applicable in group settings. After a guided, standardized induction procedure, subjects are invited to experience a series of hypnotic suggestions from easy-to-follow motoric to cognitive suggestions like posthypnotic amnesia which only few subjects experience. According to a self-rating scale about the influence experienced during these suggestions on one's behavior, suggestibility is assessed. The distribution of suggestibility in population roughly follows a bell-shaped curve (Kihlstrom, 2013; Oakley & Halligan, 2013). Suggestion-induced changes in experience and their associations in brain activity are particularly observable in subjects with high hypnotic capacity (Kihlstrom, 2013). Suggestibility positively correlates with higher brain functions like creativity, attention, vividness of imagery, inhibitory capabilities and the personality construct "absorption", which describes a state of focused, full attention requiring all resources at the expense of external orientation (Kihlstrom, 2013; Lichtenberg, Bachner-Melman, Ebstein, & Crawford, 2004; Tellegen & Atkinson, 1974). The association between high hypnotizability and superior attention could be linked to a common genetic (e.g., catechol O-methyltransferase (COMT) genotype), anatomic (e.g., enlarged corpus callosum), neurobiologic (e.g., dopamine), or neuronal (prefrontal connectivity) basis, but despite some converging evidence (Horton, Crawford, Harrington, & Downs, 2004; Lichtenberg, Bachner-Melman, Gritsenko, & Ebstein, 2000; Szekely et al., 2010; Weinberger et al., 2001), no

consistent neuronal correlates have been able to be identified to build a reliable basis for a differentiation between levels of suggestibility. Concerning electrophysiological characteristics, theta and alpha band power as a function of suggestibility and the hypnotic state have most often been focused on, due to their relation to focused attention and imagery production. Generally, increased theta and/or alpha activity was shown in highly suggestible subjects (Graffin, Ray, & Lundy, 1995; Kirenskaya, Novototsky-Vlasov, & Zvonikov, 2011; Sabourin, 1990), but results were not at all consistent. However, behavioral differences between high and low suggestible subjects robustly exist. While hypnotic suggestions impact behavior in highly suggestibles, they might not be observable in low suggestible subjects. To go even further, some studies reported posthypnotic behavior counter to suggestions in low susceptibles. This could reflect their unwillingness to be manipulated. A response to hypnotic suggestions would be inconsistent with their self-image. The fact that the success of hypnotic suggestions depends on suggestibility and expectancy of one's responsiveness (De Pascalis, Chiaradia, & Carotenuto, 2002) emphasizes the need for an evaluation of suggestibility before the application of hypnosis. Thus, in experimental research it is common practice to include high and low suggestible subjects and analyze their results separately. Otherwise, if high susceptibles follow suggestions conformably, while low suggestibles might counteract the suggestions, effects might be covered up and data misinterpreted when hypnotizability is neglected as a factor.

After having introduced the most important terms revolving around hypnosis, experimental investigations will be presented that demonstrate the purview of its effectiveness and its objective substantiation.

1.4.3. Substantiation of the hypnotic state

A multitude of experimental studies has proven hypnosis to be a versatile means effective for diverse applications from mood induction (Maccallum, McConkey, Bryant, & Barnier, 2000) or amnesia triggering (Mendelsohn, Chalamish, Solomonovich, & Dudai, 2008), to motor inhibition (Cojan, Archimi, Cheseaux, Waber, & Vuilleumier, 2013), or signal detection alteration (Jones & Spanos, 1982). Most importantly, brain imaging studies corroborate the effectiveness of hypnosis by reflecting effects on an objective level. In one study, similar brain activations during real color perception and suggested color perception in hypnosis indicated that subjective experiences in hypnosis have a basis in brain activity resembling real experience (Kosslyn, 2000). Such results hint at the existence of neuronal underpinnings of hypnotic suggestions (Kihlstrom, 2013). Even more, an additive effect of suggestions and the hypnotic state was demonstrated when comparing real experience, an imagination task and effects of suggestions given during hypnosis. Derbyshire and

colleagues (2004) demonstrated that suggested pain experience as well as real physical pain activated the pain network significantly more than mere imagination of a heat pain stimulus. Szechtman and colleagues (1998) presented comparable results for real and hallucinated versus imagined hearing. In sum, there is more to suggestions presented during hypnosis than to mere imagination. Moreover, effects are not restricted to certain modularities, but appear for visual, sensoric, and acoustic tasks. To go even further, suggestions were shown to enable dampening of automatic skills. In their study, Raz and Campbell (2011) administered a posthypnotic suggestion to participants high versus low in suggestibility telling them to ignore the meaning of the words in a Stroop test, but only focus on the colors. For both groups, comparisons to within-subject Stroop tests without posthypnotic suggestion showed a reduction in Stroop-related reaction time slowing after the suggestion, especially in high suggestibles. Thus, the posthypnotic suggestion to suppress the attribution of meaning to the words in the Stroop test inhibited automatic reading and thereby facilitated focusing on the colors. These results uncover the tremendous effect of hypnosis not only on willingly controllable processes, but also on automatic processes. This advantage is used in therapeutical and clinical contexts. Sleep induction, for instance, falls out of the range of conscious influence, as trying to take control might even result in unintended circumstances. One study experimentally examined the widely known experience that in case of an urgent want to fall asleep, sleep onset is more and more delayed. Ansfield and colleagues (1996) asked subjects to try to fall asleep while they told a control group to sleep whenever they want to. Results indicated longer sleep onset times for those asked to sleep as quickly as possible. Also in clinical settings, paradoxical intention therapy is used, aiming at taking the pressure of falling asleep from subjects by telling them to stay awake (Ascher & Turner, 1979; Espie, 1987; Ladouceur & Gros-Louis, 1986; Morin et al., 1999). Thus, to influence sleep, cognitive approaches might not be easily implemented successfully and consciousness is possibly even better circumvented. As outlined at the outset, Borkovec and Fowles (1972) and Stanton (1989) experimentally demonstrated the success of treating sleep onset problems, number of awakenings per night, and feeling of being rested in the morning with hypnotic relaxation techniques. Stanton (1999) impressively underlined the possibilities of hypnosis to treat sleep related problems with the case reports he published later (Stanton, 1999). A further investigation of the treatment effects of cognitive behavior therapy and hypnotherapy for patients with insomnia revealed significant improvements for sleep onset latency, wakefulness after sleep onset, and experienced restfulness of sleep (Schlarb, 2005).

In summary, research has not only detected neuronal correlates of hypnotic experiences, but has demonstrated its effectiveness even for unwilling, automatic processes, like sleep. So far, those few studies existing that investigated hypnotic effects on sleep patterns only measured effects superficially by subjective self-ratings. Polysomnographical measures of the effects of hypnotherapy

for treating sleep disturbances are still lacking as additional objective evidence. As outlined next, these previous studies entailed further weaknesses.

1.4.4. Weaknesses of previous studies

Despite their key role in initiating investigations on the effectiveness of hypnosis for sleep, the abovementioned studies contain diverse weaknesses which yield problematic alternative explanations for the effects. First, besides undeniable advantages of case studies, they investigate the effects in isolation and the results cannot be generalized. Thus, whether the observed effects can also be seen in other subjects is not clear. For instance, the success of treatment critically depends on the subject's responsiveness to hypnotic suggestions and is thus "limited to those patients who are able to use their imaginations in this way" (Stanton, 1999, p. 66). Thus, the sample to be investigated cannot consist of randomly selected subjects. If subjects do not believe in or do not respond to hypnosis, the effects of hypnosis are underestimated. Patients have to be willing to be hypnotized and need to be convinced of the effects of hypnosis (Deivanayagi et al., 2007). Nowadays, the inclusion of high versus low suggestible subjects is recommended and common practice (Kihlstrom, 2013; Montgomery, DuHamel, & Redd, 2000; Oakley & Halligan, 2013; Szekely et al., 2010). A further issue, common to all previous studies on the effects of hypnotic suggestions on sleep is that subjective ratings and self-reports like sleep diaries were commonly used (Stanton, 1999). This might be an interesting measure for treatment outcomes in clinical settings where improvements in subjective well-being are a crucial factor, but it cannot be excluded that demand characteristics influence the rating. Thus, it remains unclear whether subjects really had experienced an improvement or whether their rating was caused by the expectancies of the experimenters and the knowledge of the participants to have received an intervention. Although sleep belongs to a set of behaviors which cannot fully be brought under personal control and subjects could not have willingly influenced whether they follow the suggestions or not, subjective ratings might well be manipulated. As Stanton himself mentioned, the expectancy of success the patients develop before treatment is an essential component which even "may well be of more value that the specific treatment technique used" (Stanton, 1999, p. 65). Overemphasizing the effectiveness of hypnosis, however, also entails the risk of forcing an obedient subject to indicate what was expected from him. Even if no conscious will to act according to expectations was ascribed to the subjects, a biased sleep quality rating might have happened unintentionally. Studies comparing polysomnographic sleep measurements with self-ratings of sleep quality, time to fall asleep and nocturnal awakenings, show how subjects under- or overestimated their parameters in a way that allowed no correlation between sleep perception and objective recordings to be significant (Baker, Maloney, & Driver,

1999). Together, as subjective sleep ratings are easy to manipulate and even honest subjective ratings do not always reflect objective measures, the effects of hypnosis can only be demonstrated without any doubt when effects on polysomnographically measured sleep parameters can be shown. Thus, in order to weaken all alternative explanations and confirm its efficacy, effects of hypnotic suggestions on sleep urgently need to be tested objectively with polysomnography which this thesis is about to do.

1.4.5. Hypnotic suggestibility across the lifespan

Validating hypnosis as an effective treatment to influence sleep is particularly important for age-related or clinical changes in sleep, as improved sleep quality might contribute to general health in multiple ways. Additionally, due to the relationship between sleep, prefrontal functioning, and cognitive performance in the elderly, improved sleep might also support cognitive abilities (Mander et al., 2013; Wilckens et al., 2012). Regarding this critical field of possible benefits of improved sleep for healthy aging, it is obvious that the effects of hypnosis on sleep must also be investigated in the elderly. There are some reasons why a generalization from effects in younger to older adults might fail. First, it might be that older adults are less hypnotizable and more critical towards hypnosis compared to younger adults. Ehrenreich (1949) for instance reported reduced hypnotizability in older adults compared to younger adults. In contrast, a longitudinal study testing hypnotizability with a standard measure of suggestibility found quite resistant test-retest correlations over a 25-year period (Piccione et al., 1989). This suggests that hypnotizability is quite a stable trait and should thus not dramatically be influenced by age. Other variables could, however, reduce the positive effect of hypnosis on sleep in older adults. For instance it could be more challenging to alter sleep in this population. A meta-analysis comparing non-pharmacological insomnia treatments achieved smaller effect sizes in older than younger adults for effectiveness and long-lasting changes after interventions (Pallesen et al., 1998). In another study, older adults even failed to significantly improve on sleep latency after intervention, although younger adults being exposed to the same treatment did (Alperson & Biglan, 1979). Thus, the treatment potential in the elderly might be reduced compared to younger adults, and interventions might be less effective. Contrary, other meta-analyses confirmed a general efficacy of interventions in old age as well, except for certain dependent variables such as total sleep time and sleep efficiency (Brassington, King, & Bliwise, 2000). In conclusion, effect sizes of the influence that hypnosis has on sleep might be smaller in older than in younger adults. This means that if hypnosis positively influences sleep in younger adults, it cannot be inferred without any doubt that this tool is also effective in the elderly. Therefore, the third manuscript will try to replicate the effects of hypnotic suggestions on SWS in an elderly sample. A

further aim of this manuscript is to examine the consequences of deepened sleep for memory. Theories attribute a restorative function of deep sleep to prefrontal activity, which will be tested by introducing a verbal fluency task before and after sleep. Additionally, the strength of the relationship between sleep and memory consolidation is supposed to weaken with age. Comparing the retention benefit across sleep between younger and older adults might shed light on this issue. Based on the theoretical considerations outlined before, benefits for prefrontal dependent memory tasks and memory consolidation should be expected if SWS can be increased successfully.

1.4.6. Interim summary

To sum up, the relationship between sleep and memory can be used practically. Improvements in sleep are suggested to benefit memory performance. A non-pharmacological approach to influence sleep is hypnosis. This is a state of altered consciousness in which suggestions can be given to elicit changes. Experimental studies have demonstrated the effectiveness of this procedure in diverse fields and have also confirmed its influence on sleep. Thus, multiple functions are attributed to hypnosis. Firstly, hypnosis could be used as a valuable non-drug tool to manipulate sleep for fundamental research into sleep effects on memory. Avoiding the influence of drugs on sleep and any side effects diminishes the risk of uncontrolled effects. Secondly, hypnosis could be used as a drug-free intervention applicable for age-related sleep changes. Older adults' memory impairments, sleep complaints, and co-occurring impairments of daytime functioning and health could be reduced with hypnosis instead of medication. The second and third manuscript will be concerned with these issues. Before presenting the manuscripts, a short repetition of methodological key aspects and the concrete hypotheses will be provided in the last paragraph on Methods.

2. General Methods

This paragraph aims at building up a basis for understanding the methods applied in the following manuscripts as well as their advantages and the reasons for their implementation. Therefore, more detailed information concerning the methods will be presented in the following sections. The induction of memory reactivations during sleep and the challenge of memory stability with an interfering task will be outlined first. Thereafter, the concrete techniques used in our hypnosis will be delineated.

2.1. Induction of Memory Reactivations and Interference Testing

In the first manuscript, memory will be externally reactivated during different sleep stages by presenting odors associated with the learning context. This triggered replay is termed induced memory reactivation. An olfactory stimulus is presented during the encoding of a 2-D object-location task. The simultaneous presentation establishes an association between the learning situation and the odor. This link is used for reactivating the learning situation during sleep. As Rasch et al. (2007) have shown, applying an odor as a cue during SWS reminds the system of the learning situation and even elicits activation in the brain networks which were involved during information acquisition, i.e. the hippocampus. This not only demonstrates hippocampal sensitivity, but also the access that odors have to the hippocampus. This is due to the special way the cortical processing of olfactory information is organized. Different from other sensory information, odors bypass thalamic gating and can directly reach higher-ordered structures like the hippocampus (Zelano & Sobel, 2005). Declarative memories, processed in the hippocampus, can thus directly be modulated by incoming olfactory cues (Rasch et al., 2007). Furthermore, and probably related to this way of processing, in contrast to other cueing stimuli olfactory stimuli enjoy a particular benefit. Their presentation is not reliably able to alert a sleeper (Carskadon & Herz, 2004). This is a fundamental requirement when reactivations are triggered during sleep and therefore olfactory reminder cues were implemented in our study.

In order to test the degree of stabilization after reactivation, mere comparison of memory performance after retention intervals with and without induced reactivations is not sufficient. Therefore, Ellenbogen et al (2009) and Diekelmann et al (2011) additionally introduced an interfering task before post-sleep recall. This directly probes how stable memory is immediately after having been reactivated (or not) during the sleep period. This method had already been used to uncover the brain state dependent function of reactivations for stabilization and was therefore chosen for

investigating the effect of induced reactivations during REM sleep for memory stability in the first study. According to the night half paradigm, reactivations were induced in the second night half in order to disentangle the effects of SWS and REM sleep on memory. After the first three hours of SWS-rich night-time sleep, subjects learned the memory task in the presence of the odor, which was redelivered during the late, REM sleep-rich night half.

2.2. Hypnosis

The induction procedure that was used to elicit the hypnotic state started with eye fixation and attention focusing on external sensory. For instance, attention was drawn to the EEG cap the subjects wore during listening and the sounds or noise from outside the sleep cabin. This was followed by a gradual induction with 10 steps leading deeper into relaxation. We thus included common induction procedures used in hypnotherapeutic settings (Revenstorf, 2010). For suggesting deep sleep, we assumed a wider acceptance of indirect suggestions and implemented a metaphor of a fish swimming in the sea, plunging deeper and deeper into the ocean, relaxing more and more. Words like “deep” and “slow” were included to prompt slow-wave sleep and relaxation. Possibly, for some of the elderly generation, the more direct form of suggestion as used in classical hypnosis would be more advantageous, as uncertainties are suppressed by clear commands. However, we felt that, considering the existing skepticism towards hypnosis, it might be less frightening when indirect suggestions are used instead of subjecting participants to concrete orders. We recorded the hypnosis on a tape to ensure a standardized procedure for every participant. Although individually tailored metaphors could be more efficient, standardization has a higher priority when comparing experimental groups. The fundamental and experimental direction of the investigation was also the reason for the inclusion of healthy participants. The meta-analysis of Ohayon et al (2004) showed that even mild or moderate disorders or illnesses have the power to blur effects. Although being based on studies including non-clinical samples, the authors observed diminished effect sizes in groups including “some not perfectly healthy subjects” (p.1270) compared to a sample controlled for several medical and mental illnesses. Clinical samples often include patients with diverse comorbidities. This lowers homogeneity and comparability and makes data harder to interpret. The inclusion of patients is rather appropriate in clinically focused research. Another methodological issue is that as healthy young adults generally have a good night-time’s sleep, further improvements are hard to achieve. Thus, we decided to test midday naps in subjects not used to have a nap during the day. This artificially increased the difficulty to fall asleep and to maintain sleep for 90 minutes. This time period is enough to observe possible effects of sleep on memory as shown before (Alger, Lau, & Fishbein, 2012; Korman et al., 2007; Lahl et al., 2008; Mednick, Nakayama, & Stickgold, 2003).

Further, as sex has a tremendous influence not only on sleep, but also on memory, only females were recruited to avoid gender effects (Fukuda et al., 1999). As in general, vast inter-individual differences in sleep, and particularly in SWS and SWA exist (Dijk, 2009), it was vital to apply a within-subjects design, comparing two sleep periods within the same person. Of course, suggestibility was measured and split the sample into subjects high versus low in suggestibility.

Having outlined the methods in more detail, the following last section will prepare for the three manuscripts by shortly summarizing the respective hypotheses.

3. Hypotheses

This section aims at summarizing the research questions outlined above which will be investigated in the three manuscripts.

Manuscript 1. Reactivations occurring in REM sleep are hypothesized to stabilize declarative memory, but this has not been confirmed experimentally yet. Contrary to this, as REM sleep lacks N2/SWS characteristics, while mainly shares commonalities with wakefulness during which reactivations destabilize memories, we expected that reactivation during REM will not lead to memory stabilization. Due to these diverging hypotheses, we test the effects of induced memory reactivations during REM sleep on the stability of declarative memory in manuscript 1.

Manuscript 2. If spontaneous reactivations in SWS benefit memory consolidation, increased time spent in SWS should enhance memory consolidation. Hypnosis has proven effective to treat sleep disturbances. Effects on objective parameters that support these findings are, however, still lacking. Therefore, we investigated whether a hypnotic suggestion to sleep deeper can increase the amount of objectively measured SWS during a midday nap in healthy young females. We hypothesize that hypnotic suggestions deepen sleep. Further we assume that higher levels of SWS benefit memory consolidation.

Manuscript 3. Sleep is vital for diverse aspects of health and subjective well-being, but its quality declines across lifespan. Specifically, declines in SWS parallel losses in memory performance. Thus, developing a drug-free tool to improve sleep is highly relevant in the elderly. As the degree of effectiveness of hypnosis obtained in younger adults might not be conferrable to an elderly sample, the study depicted in manuscript 2 will be replicated with older adults in manuscript 3. Further, to test the benefit of slow-wave sleep for frontal functionality, memory tasks associated with prefrontal activity were assessed before and after sleep. We hypothesize that sleep can be deepened by hypnotic suggestions also in the elderly as well. We further expect this to improve prefrontal dependent memory performance and consolidation.

4. Manuscripts

4.1. No Effect of Odor-Induced Memory Reactivation during REM Sleep on Declarative Memory Stability[1]

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All authors declare no conflict of interests

[1] A similar version of this manuscript has been published in „Frontiers in Systems Neuroscience"

Abstract

Memory reactivations in hippocampal brain areas are critically involved in memory consolidation processes during sleep. In particular, specific firing patterns of hippocampal place cells observed during learning are replayed during subsequent sleep and rest in rodents. In humans, experimentally inducing hippocampal memory reactivations during slow-wave sleep (but not during wakefulness) benefits consolidation and immediately stabilizes declarative memories against future interference. Importantly, spontaneous hippocampal replay activity can also be observed during rapid eye movement (REM) sleep and some authors have suggested that replay during REM sleep is related to processes of memory consolidation. However, the functional role of reactivations during REM sleep for memory stability is still unclear. Here, we reactivated memories during REM sleep and examined its consequences for the stability of declarative memories. After three hours of early, slow-wave sleep (SWS) rich sleep, 16 healthy young adults learned a 2-D object-location task in the presence of a contextual odor. During subsequent REM sleep, participants were either re-exposed to the odor or to an odorless vehicle, in a counterbalanced within subject design. Reactivation was followed by an interference learning task to probe memory stability after awakening. We show that odor-induced memory reactivation during REM sleep does not stabilize memories against future interference. We propose that the beneficial effect of reactivation during sleep on memory stability might be critically linked to processes characterizing SWS including, e.g., slow oscillatory activity, sleep spindles or low cholinergic tone, which are required for a successful redistribution of memories from medial temporal lobe regions to neocortical long-term stores.

Keywords

rapid eye movement sleep, reactivation, memory stability, hippocampus, declarative object location task

Introduction

The fate of a memory after its reactivation strongly depends on the state of the brain. In the brain state of slow-wave sleep (SWS), memories are spontaneously reactivated, and several studies have successfully shown that inducing reactivations during SWS by a reminder activates hippocampal brain areas and improves later memory recall using odors or sounds (Antony, Gobel, O'Hare, Reber, & Paller, 2012; Diekelmann, Büchel, Born, & Rasch, 2011; Oudiette & Paller, 2013; Rasch, Büchel, Gais, & Born, 2007; Rihm, Diekelmann, Born, & Rasch, 2014; Rudoy, Voss, Westerberg, & Paller, 2009). In contrast, inducing reactivations in a waking brain state by a reminder or active retrieval attempts can lead to a modulation or even forgetting of memories when memory stability is challenged by interfering agents (Nader, Schafe, & Le Doux, 2000; Walker, Brakefield, Hobson, & Stickgold, 2003), requiring a period of reconsolidation of the memory in order to persist (Nader & Hardt, 2009).

It is assumed that the memory-strengthening effect of hippocampal reactivations during SWS is supported by redistribution of memory representations from hippocampal to neocortical networks in close coordination with SWS specific hippocampal sharp-wave ripples, sleep spindles and slow oscillations (Rasch & Born, 2013). Thereby, hippocampal dynamics and hippocampal-neocortical feedback loops seem to critically depend on a low level of the neurotransmitter acetylcholine, which is characteristic for SWS. Reactivations in this milieu face beneficial conditions for initiating plastic changes in neocortical brain areas (Gais & Born, 2004; Hasselmo & Giocomo, 2006; Rasch, Born, & Gais, 2006). In contrast, levels of acetylcholine are elevated during wakefulness, which may hinder successful consolidation and redistribution of reactivated memories (Hasselmo & Giocomo, 2006). Furthermore, prefrontal process of retrieval monitoring specific for wakefulness might render memories susceptible to interference.

Spontaneous reactivations do not only appear during SWS or wakefulness, but also in the brain state of rapid eye movement (REM) sleep. Neuronal firing patterns in the hippocampus having been active during learning were also active during REM sleep (e.g., Louie & Wilson, 2001). As REM sleep shares several features with waking, including a waking like brain activity and a high cholinergic tone, spontaneous memory reactivations during REM sleep might not be beneficial for memory consolidation. However, several authors have implicated REM sleep and memory reactivations during REM sleep in processes of memory consolidation: first, there is quite consistent evidence from animal studies that REM sleep plays a role in memory consolidation (for a review see Fishbein & Gutwein, 1977). Second, inducing reactivations during REM sleep in animals using fear conditioning procedures in fact improved consolidation of fear (see Hennevin, Huetz, & Edeline, 2007, for a review). Thus, it was suggested that the hippocampal reactivations reflect or contribute to memory

processing during REM sleep (Hennevin, Hars, Maho, & Bloch, 1995). However, in contrast to waking and SWS, the consequences of reactivation during REM sleep on memory stability in humans are still unclear.

Here we specifically tested the effect of reactivating hippocampus-dependent, declarative memories during REM sleep on later memory stability including an interference learning task after reactivation. Importantly, we focused on late, REM sleep rich sleep to exclude confounding effects of prior SWS on memory stability. In contrast to the positive effects of cueing during REM sleep in animals, we predicted that inducing reactivations during REM sleep does not stabilize memories against future interference, because important features critical for a beneficial effect of reactivation on memory consolidation (i.e., hippocampal sharp-wave ripples, slow oscillations, sleep spindles and a low cholinergic tone) are lacking during REM sleep.

Materials and methods

Subjects

Sixteen healthy, non-smoking young adults, aged 20 to 34 (23.9 ± 4.02 years, 10 females) were tested in a counterbalanced within subject design. None of the participants reported any irregular sleep-wake cycles, shift working, neurological, psychiatric or endocrine disorders or took any sleep modulating medication. Subjects reported normal sleep (Pittsburgh Sleep Quality Index PSQI < 6) and had neither a nasal infection nor ingested any caffeine or alcohol on the experimental day. They were asked to get up between 7:00 and 8:00 a.m. on experimental days. Subjective reports indicated similar bedtimes (i.e., close to midnight) two days before the experiment for the two experimental conditions, suggesting that participants were in the same circadian rhythm in both conditions. All subjects spent an adaptation night in the sleep laboratory including placement of the nasal mask and electrodes as during the experimental nights. Two subjects were excluded from analyses due to chance level performance at interference learning, and one subject due to learning performance diverging by more than 2 SD from group mean. Subjects gave written informed consent to their participation and were paid 200 Swiss francs. The ethics committee of the University of Zurich approved the study.

Design and procedure

Subjects spent one adaptation night and two experimental sessions in the sleep laboratory. They were fully informed about the session flow. The experimental sessions were separated by at

least 7 days. The sessions started at 9:00 p.m. with the attachment of electrodes for electroencephalographic (EEG), electromyographic (EMG) and electrooculographic (EOG) recordings. After filling out standard questionnaires and performing a reaction time test, subjects were allowed to sleep for at least 3 hours from 10:30 p.m. on (see Figure 1). Fifteen minutes after awakening, at about 2:00 a.m., participants first performed a reaction time task and an odor detection test to ensure functionality of the olfactometer. Participants then learned the 2-D object-location task in the presence of the odor before they performed the odor detection test and the reaction time task again. Thereafter, participants returned to bed and olfactory stimulation (using a repeated 30-s on / 30-s off pattern) was started as soon as polysomnographic recordings indicated stable REM sleep. We stimulated during tonic and phasic REM sleep phases. On one night, participants were re-exposed to the same odor that had been present during prior learning to induce memory reactivation. On the other night, an odorless vehicle stimulus was applied, in a counterbalanced order. Neither the subject nor the experimenter knew about the order of the stimulation. Stimulation was stopped as soon as arousals, awakenings or shifts into other sleep stages were detected. On average, stimulation duration during sleep was 29.77 ± 1.86 minutes (range 18 to 45.5 minutes) following Diekelmann et al.`s (2011) protocol. Post-experimental offline scoring confirmed that 92.55 ± 1.89 % of odor stimulation and 92.29 ± 2.98 % of placebo stimulation actually took place during REM sleep. Participants were awakened directly after the last reactivation in the REM sleep phase. Shortly after awakening, participants learned the interference 2-D object-location task. After a break of 20 minutes, recall of the card-pair locations of the original task, learned before sleep, was tested. Participants were asked to perform as well as possible in each of the memory tasks.

Figure 1. Experimental Procedure

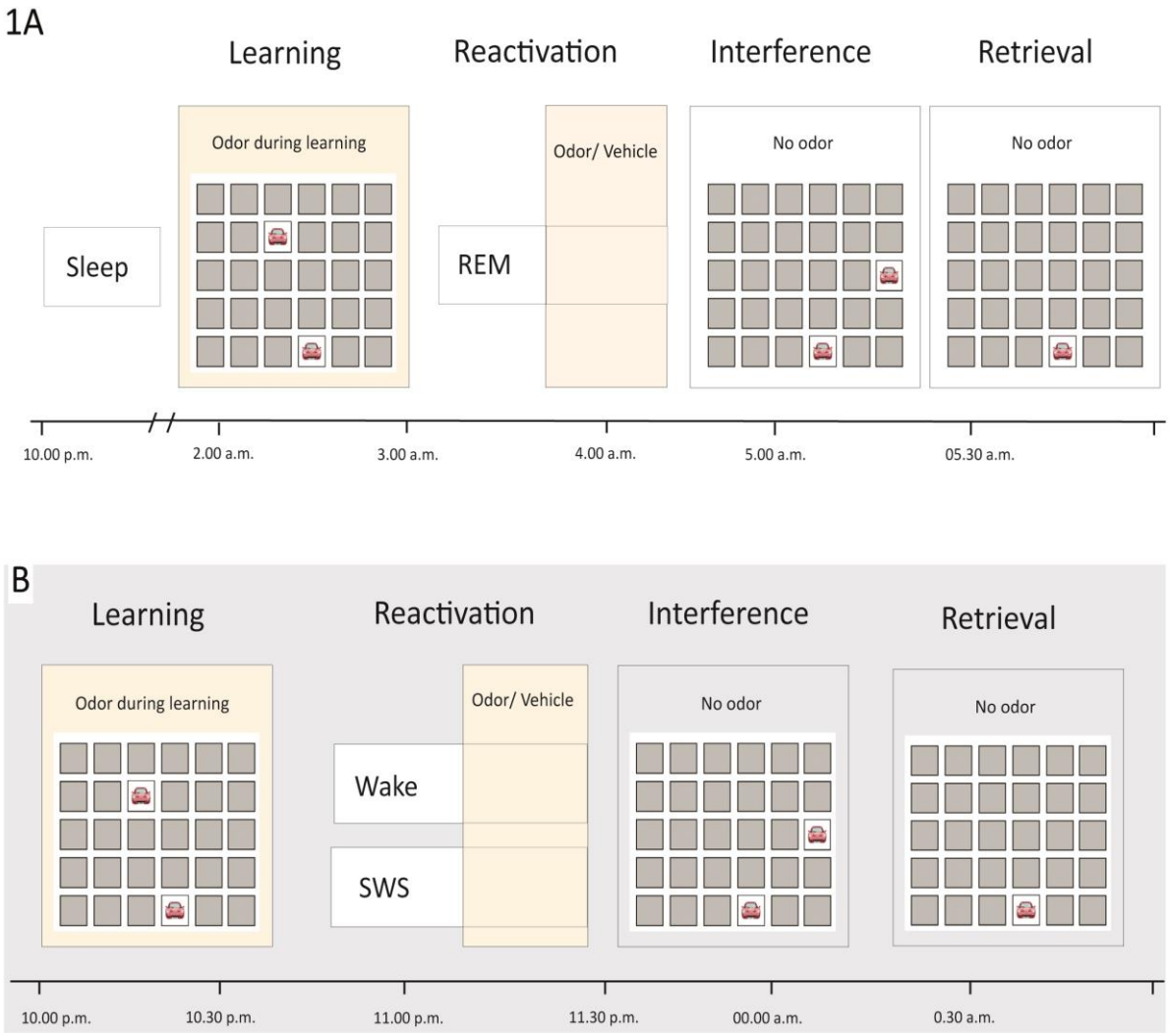

Figure 1. Experimental procedure. (A) Subjects slept for approximately 3 hours before learning a 2-D object-location task while being exposed to an odor. During subsequent REM sleep, either the same odor or an odorless vehicle was presented for at least 20 minutes, in a counterbalanced order. After awakening, subjects learned an interfering 2-D object-location task without odor presentation. Retrieval of the original task was tested thereafter. (B) Reactivation in Diekelmann et al.'s (2011) study, in contrast, occurred either during SWS or wakefulness.

Odor delivery and substance

Odor and placebo were delivered by a computer-controlled olfactometer as described previously (see Rasch et al., 2007, for details). The olfactometer was placed outside the sleep cabins and was connected to the nasal masks via Teflon tubes, such that the subject was not disturbed by any noise accompanying the stimulation procedure. The odor was isobutyraldehyde, diluted in 1,2-propanediol at a concentration of 1:200 (as used in Diekelmann et al., 2011). Odorless propanediol alone served as placebo.

2-D object-location task

The two-dimensional object-location memory task, resembling the game "concentration", was used as described previously (see Diekelmann et al., 2011; B. Rasch et al., 2007, for details). Learning consisted of remembering the location of 15 card pairs displaying animals and everyday objects on the computer screen. Card pairs were uncovered sequentially during learning phase until all pairs had been shown twice. Thereafter, the first card of each card pair was uncovered and subjects were required to indicate the correct position of the second card by a mouse click on the respective field. Feedback was provided indicating the correct location of the second card. This cued recall procedure was repeated until at least 60% of responses were correct. The odor presentation during learning was event-locked, being initiated with onset of the presentation of the first card and enduring until the presentation of both cards was discontinued. The final recall of this task after sleep was similar to the cued recall procedure during learning except that no odor was presented and that only one cued recall trial was administered. As dependent variable ("memory retention across sleep"), the relative amount of correctly retrieved card pair locations was used, with performance at learning set to 100%.

Interference learning was conducted with the same task, including the same card pairs, but the position of the second card of each pair was changed. No odor was presented during interference learning and there was only one single cued recall trial following learning. For the two experimental sessions, two parallel versions of both, the object-location task as well as its interference equivalent, were used. Parallel versions included different pictures.

Vigilance and subjective sleepiness

Reaction times were assessed in a reaction time task before the first sleep episode, before and after learning as well as after recall of the original 2-D object-location task to assess general alertness. A red dot randomly appeared on a screen and subjects had to press the space key as soon as they recognized the dot. Forty five trials were included. Subjective sleepiness was assessed using the Stanford Sleepiness Scale before the first sleep period and at the end of the experimental session.

Cortisol measures

Cortisol was measured with saliva tests (Sarstedt, Germany). Saliva cortisol concentrations were measured using a commercially available luminescence immune-assay (IBL, Hamburg, Germany) with intra- and interassay coefficients of variation < 5%. Cortisol measures were taken

before and after the first and second night half and after recall of the original 2-D object-location task at the end of each experimental session.

Polysomnographic recordings

EEG was recorded from three scalp electrodes (Fz, Cz, and Pz according to the international 10-20 system) and an averaged mastoid reference. Data was prepared using the VisionAnalyzer 2.0 (Brain Products, Germany) and filtered according to the settings suggested by the American Academy of Sleep Medicine (AASM). Additionally to the online scoring of sleep stages, sleep was scored offline using 30 s periods according to standard criteria (Iber, Ancoli-Israel, Chessonn, & Quan, 2007) as wake, sleep stages N1-N3 and REM sleep, by two sleep experts.

For a more fine-grained analysis of sleep during the second night half power spectral analyses were run on EEG recordings during NonREM and REM sleep. Data of 30 s of sleep were segmented into artifact-free blocks of 4096 data points (≈ 8.2 s) with an overlap of 409 data points, respectively to achieve a resolution of 0.2 Hz. Before calculating power using fast Fourier transform, a Hamming Window of 10 % was applied on the data points. Individual area (μV * ms) information was determined for slow-wave activity (SWA) during NonREM (1 – 4.5 Hz), theta during REM sleep (4.5-8 Hz), and slow (11 – 13 Hz) and fast spindles (13 – 15 Hz) during NonREM sleep.

REM analysis

REM density was calculated by dividing the number of 1-s periods during REM sleep that contained rapid eye movements by the total number of 1-s REM sleep epochs (Ficca et al., 2004). Rapid eye movements were detected automatically as rapid changes in the EOG signal (> 0.8 mV/s) after movement artefact rejection.

Statistical analyses

Data was analyzed using paired t-tests including the factor “Reactivation” (odor vs. placebo). For the critical investigation of the differential influence of brain state on memory stability, a comparison of data with the previous study (Diekelmann et al., 2011) was conducted with a repeated measures ANOVA with the within-subjects factor “Reactivation” (odor vs. placebo) and the between-subjects factor “Study” (SWS vs. wake vs. REM) on recall performance. The level of significance was set to $p = .05$. Greenhouse Geisser corrections were used whenever indicated by significant tests of sphericity. For descriptive values, mean ± SEM are indicated.

Results

Effect of induced memory reactivation during REM sleep on memory stability

In contrast to the hypothesis of the beneficial role of memory reactivations during REM sleep, inducing reactivations during REM sleep had no influence on memory stability. After odor-induced memory reactivation during REM sleep, participants remembered 54.16 ± 5.93 % of the learned locations, whereas they correctly recalled 52.86 ± 6.49 % after presentation of the odorless vehicle stimulus (p = .87, Figure 2a and Table 1). Learning performance (number of recalled card pairs at the end of learning) did not differ significantly between the two conditions (9.92 ± 0.26 vs. 10.69 ± .37, p = 0.13) and learning of the interference task was also highly comparable (6.07 ± 0.83 vs. 5.67 ± .82, p = 0.72).

In addition, we directly compared the effects of REM sleep reactivation on memory to the results of the SWS reactivation condition and waking reactivation condition from our previous study (Diekelmann et al., 2011). The learning and odor-induced reactivation protocol was identical in both studies (Figure 1b). However, time of learning was 10:00 p.m., and retrieval took place at around 0:30 a.m. in the previous study, thus examining a period of early SWS rich sleep versus a corresponding waking interval, in contrast to the late REM sleep rich interval in the present study. Descriptively, the odor reactivation-induced influence on memory stability (in comparison with placebo) was +23.38 ± 5.48 % for reactivation during SWS, 1.30 ± 8.01 % for reactivation during REM sleep and -17.96 ± 6.37 % for reactivation during waking (F(2, 34) = 9.03, p = .001, eta^2 = .35). This expressed itself in a significant interaction when comparing the REM sleep reactivation with the SWS reactivation group, which indicated a robust stabilizing effect of memory reactivation during SWS that was not evident after reactivation during REM sleep (F(1, 23) = 5.00, p = .035, eta ^{2} = .18; Figure 2). There was also a statistical trend for the interaction between reactivation during REM sleep as compared to waking, with a destabilization of memories after reactivation during wakefulness but not during REM sleep (F(1,23) = 3.47, p = .08, eta ^{2} = .13). Generally, SWS as well as waking groups outperformed participants in the REM sleep group in recall of card pairs independent of reactivation or placebo conditions (main effect F(2, 34) = 9.10, p = .001, eta ^{2} = .35).

Figure 2. Data of Memory Performance

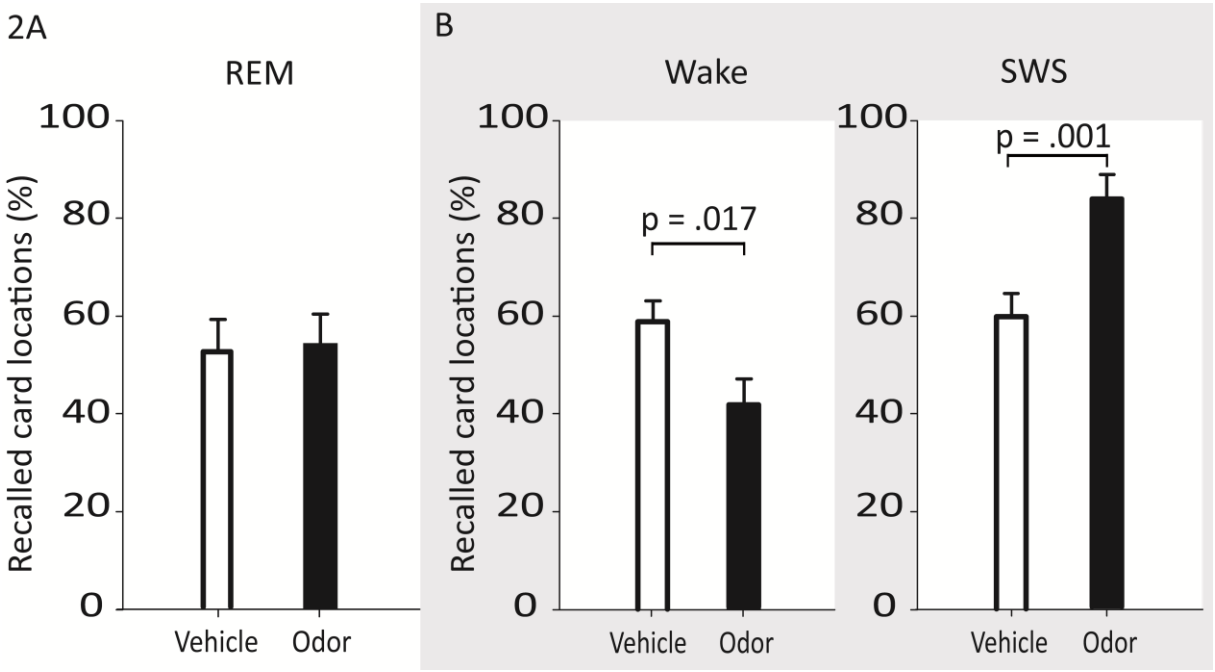

Figure 2. Recall of card locations (%) was not differentially affected by interference learning after reactivation in REM sleep (A), but showed impairments after reactivation during wakefulness and enhanced resistance towards interference after reactivation in SWS (B, data adapted from Diekelmann et al. 2011). Values are means ± SEM.

Table 1. Performance on the 2-D Object-Location Task

	Odor	**Placebo**	***p***
Learning	9.92 ± .26	10.69 ± .37	.13
Number of trials	3.39 ± .58	2.54 ± .45	.10
Absolute change	- 4.62 ± .66	-5.00 ± .69	.68
Relative change	54.16 ± 5.93	52.86 ± 6.49	.87
Interference learning	6.07 ± .83	5.67 ± .82	.72

Notes. Absolute recall performance during learning of the original object-location task, number of trials needed to reach criterion, absolute and relative change from learning to retrieval, and absolute recall performance during learning of the interference task. Mean ± SEM are indicated.

Control variables

There were no differences in encoding of the original memory task between the studies ($F(2, 34) = 0.43$, $p = 0.66$ for number of remembered pairs, $F(2,34) = 0.56$, $p = 0.58$ for number of trials). Furthermore, learning of the interference task also did not differ significantly between the REM sleep group (5.89 ± 0.62) and the SWS group (5.63 ± 0.65), $t(23) = -0.31$, $p > 0.76$. As reported previously, interference learning in the wake group was better than in the sleep groups (9.13 ± 0.65, $F(2,34) =$

9.10, p = 0.001), which was already ruled out as confounding factor by a subgroup analysis with matched interference learning performance (Diekelmann et al., 2011). We observed no difference in sleep stage distribution between odor and placebo condition, neither during late REM sleep rich sleep during which olfactory stimulation was applied (all $p \geq 0.14$, see Table 2 for descriptive values) nor during early SWS rich sleep before learning (all $p \geq 0.23$). Furthermore, we did not find any significant differences between reactivation and placebo nights in oscillatory power for the theta band during REM sleep ($p \geq 0.31$) or for the SWA ($p \geq 0.23$), slow spindle ($p \geq 0.11$) and fast spindle bands ($p \geq 0.15$) during NonREM sleep in none of the electrodes (i.e., Fz, Cz, Pz). In addition, there were no significant differences between odor and placebo conditions in REM density (p = 0.18), 1 second segments in which eye movements occurred (p = 0.64), subjective sleepiness ratings ($p \geq .78$), reaction times during learning and retrieval (all $p \geq 0.24$), cortisol levels ($p \geq 0.08$), or odor detection before and after learning ($p \geq 0.17$) (see Table 3). Finally, memory retention differences between both nights did neither correlate with the difference in sleep stages ($p \geq 0.08$) nor the difference in each of the control variables ($p \geq 0.23$). Further, neither REM density (p = 0.76) nor number of segments in which eye movements occurred (p = 0.24) during odor presentation correlated with the recall memory performance of the original task after sleep.

Table 2. Sleep Stages for the Early Night (Before Learning) and Late Night (After Learning With Odor/Placebo Stimulation)

Sleep stages (in minutes)	**Early night**			**Late night**		
	Odor	**Placebo**	***p***	**Odor**	**Placebo**	***p***
Wake	2.41 ± 1.53	8.69 ± 4.74	.24	4.27 ± 2.24	4.46 ± 1.95	.94
N1	8.89 ± 1.13	9.50 ± 1.95	.73	11.00 ± 2.20	9.77 ± 1.95	.54
N2	71.46 ± 5.87	66.54 ± 7.13	.49	65.12 ± 8.67	62.19 ± 5.43	.76
N3	89.31 ± 5.62	89.89 ± 10.63	.96	20.69 ± 4.16	32.156 ± 6.52	.14
REM	24.89 ± 3.18	20.00 ± 2.79	.23	35.62 ± 3.02	36.23 ± 4.11	.88
Sleep latency	20.96 ± 6.80	16.96 ± 3.84	.44	19.35 ± 2.42	23.31 ± 4.55	.42
SWS latency	14.27 ± 1.60	18.73 ± 5.77	.40	40.85 ± 9.75	39.35 ± 11.47	.90
REM latency	106.31 ± 11.76	117.00 ± 11.76	.46	64.04 ± 5.22	57.65 ± 4.52	.26

Notes. Mean ± SEM are indicated.

Table 3. Values of the Control Variables Before and After Early and Late Sleep

	Before			After		
Early sleep	**Odor**	**Placebo**	***p***	**Odor**	**Placebo**	***p***
Objective vigilance (RT)	273.53 ± 10.34	267.90 ± 9.76	.55	282.86 ± 15.30	271.92 ± 12.42	.42
Cortisol level	2.75 ± .57	2.72 ± .36	.97	3.24 ± .50	2.06 ± .36	.08
Late sleep						
Objective Vigilance (RT)	279.50 ± 13.45	275.57 ± 11.51	.59	281.45 ± 13.42	276.02 ± 12.03	.24
Cortisol level	7.04 ± 1.54	6.45 ± 1.13	.67	13.65 ± 2.60	10.59 ± 2.26	.38
Subjective sleepiness	3.08 ± .18	3.15 ± .19	.78	3.31 ± .29	3.31 ± .35	>.99
Odor detection level	8.92 ± .21	9.39 ± .27	.17	8.77 ± .32	8.85 ± .34	.82

Notes. Mean ± SEM are indicated. Values for objective vigilance and cortisol measures are indicated for the measures before the first and second sleep period. Subjective sleepiness was measured before the first sleep period and in the morning after the second sleep period. Odor detection was measured before and after the second sleep period in which reactivation took place.

Discussion

In contrast to several studies suggesting a functional role of reactivations during REM sleep for memory consolidation, inducing reactivations of hippocampus-dependent, declarative memories during REM sleep by memory-associated odors did not improve later memory resistance. In this respect, our data is in line with previous studies attributing no specific role of REM sleep in sleep-dependent processes of declarative memory consolidation (Rasch et al., 2007). Several studies using night-half paradigms have consistently shown that declarative memories benefit from early, SWS rich sleep, but not from late, REM rich sleep (Plihal & Born, 1997). Furthermore, selective REM sleep deprivation typically does not impair declarative memory consolidation (Chernik, 1972; Lewin & Glaubman, 1975). However, some reports of hippocampal memory reactivation during REM sleep exist (Louie & Wilson, 2001; Poe, Nitz, McNaughton, & Barnes, 2000), and REM-associated dreaming activity has been long suspected to play a role in processes of memory consolidation (Crick & Mitchison, 1995). Despite the possible existence of spontaneous memory reactivation during REM sleep, here we show that experimentally inducing reactivation does not stabilize declarative memories. Importantly, we used an established paradigm which resulted in improved memory when the odors were applied during SWS as now shown in three independent studies (Diekelmann et al., 2011; Rasch et al., 2007; Rihm et al., 2014). Enhanced memory performance (Rasch et al., 2007) and stability (Diekelmann et al., 2011) after induced memory reactivation with the learning-associated

odor during SWS were accompanied by hippocampal brain activations. According to the active system consolidation account, sleep-dependent memory consolidation depends on a close interaction between hippocampal memory reactivation, slow oscillations, and sleep spindles resulting in a strengthening and reorganization of memories during sleep (Rasch & Born, 2013). Besides the lack of slow oscillations and sleep spindles during REM sleep, the high acetylcholine level during REM might explain why the induction of reactivation during this sleep stage does not stabilize memories. During SWS, hippocampal reactivations are assumed to feed back to neocortical areas to initiate plastic changes in neocortical brain areas involved in long-term memory storage. It is assumed that the disinhibition of these feedback projections critically depends on low levels of the neurotransmitter acetylcholine, prevalent during SWS (Hasselmo & Giocomo, 2006; Rasch et al., 2006). This is supported by studies showing that the increase of acetylcholine during SWS completely blocks declarative memory consolidation (Gais & Born, 2004). Thus, this transmitter milieu of low cholinergic tone seems to be a prerequisite for the beneficial role of spontaneous and induced reactivations on memory stability. Future studies still need to test, which of these parameters are responsible for the lack of the beneficial effect of reactivations during REM sleep for memory stability.

Interestingly, although REM sleep shares several features with the wake state, inducing reactivation during REM sleep did also not destabilize memories as observed in reconsolidation studies during waking (Nader & Hardt, 2009). It can be speculated that waking consciousness, awareness, and a functional “encoding mode” might be important factors contributing to a destabilization of memories after reactivation. For example in rats, inhibition of protein synthesis during wakefulness blocked memory reconsolidation only when new encoding of information was involved during the time of reactivation (Morris et al., 2006). This encoding mode might be reflected in the prefrontal activations following memory reactivation during wakefulness as was shown in Diekelmann et al. (2011). Thus, reactivation might only induce a destabilization of memories when conscious encoding of new information occurs simultaneously, possibly even merely in case of a “conflict” between new and reactivated information and a need for an “updating” of the reactivated information with respect to the new one. In contrast, no new or conflicting information is simultaneously encoded during REM sleep, which might explain the lack of reactivation-induced destabilization during this sleep stage.

It might be argued that odors are not capable of reactivating memories during REM sleep. We consider this explanation unlikely, because odors administered during REM sleep are readily processed, can influence dreams (Trotter, Dallas, & Verdone, 1988) and can be conditioned to preceding tones (Arzi et al., 2012). In addition, previous studies have shown that memories can be reactivated during REM sleep using fear-conditioned tones in animals (see Hennevin et al., 2007, for

a review). Importantly, several studies implicate REM sleep in procedural and emotional learning processes (Nishida et al., 2009; , for reviews see Smith, 2001; Rasch & Born, 2013), and it might be possible that reactivation of emotional memories or procedural memories during REM sleep (instead of neutral declarative memories) benefits their consolidation.

Of particular note is that we specifically tested effects on memory stability after REM sleep reactivations. Thus, our data does not exclude other memory functions of reactivations during REM sleep. For instance, Sterpenich et al. (2014) similarly showed no effect of reactivations during REM sleep on general recognition performance. However, reactivating memories during REM sleep increased both hit rates as well as false alarm rates and changed the associated neural activity during recognition testing. The authors concluded that reactivations during REM sleep might modify memory traces resulting in a better integration and establishment of associative connections. Our data does not contradict this interpretation.

Independent of the reactivation effect, general recall performance after sleep was lower in the present compared to our previous study, possibly due to different times of encoding, consolidation and recall of the original object-location task and learning of the interference task (Figure 1). However, despite different times of learning and possible concomitant, confounding circadian influences and prior sleep effects, we did not find performance differences in encoding performance. Moreover, consolidation in the current study occurred during a late REM sleep rich sleep interval, which per se is typically not beneficial for declarative memories (Rasch & Born, 2013). Furthermore, elevated levels of cortisol in the morning might have hindered memory recall while supporting learning of the interference memory (Wolf, 2009). Finally, participants slept longer in the current than in the previous study and thus, the length of the retention interval was different (138 min vs. 40 min). However, we did not find any significant correlation between sleep duration and recall performance. Importantly, the effect of REM sleep reactivation on memory stability per se depends on the comparison within one and the same study (i.e., reactivation vs. placebo), rendering confounding effects of the above-mentioned factors rather unlikely. Further it must be considered that participants still performed at a rather high level, excluding bottom effects or performance at chance level.

In sum, our study provides no evidence for an effect of reactivation during REM sleep on the stabilization of declarative memories. Even though spontaneous memory reactivations might exist during REM sleep, they might have no functional effect on stabilizing processes of declarative memory consolidation during sleep. Our results suggest that this might depend on SWS specific events like slow oscillations or spindles or the low cholinergic tone during SWS. Future studies need to test whether emotional or procedural memories benefit from inducing memory reactivations

during REM sleep. Furthermore, other qualitative memory changes might have resulted from reactivations, which were not measurable with our design.

Acknowledgements

We thank Fatime Bislimi and Pascal Kröni for assistance in data collection. This work was supported by a Grant of the Swiss National Foundation (SNF) (PP00P1_133685) and the Clinical Research Priority Program (CRPP) “Sleep and Health” of the University of Zurich.

Author contributorship

M.C., S.D. and B.R. designed the experiment, M.C. collected the data, M.C., S.D. and B.R. analyzed the data. All authors wrote the manuscript, discussed results and approved the final version.

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4.2. Deepening Sleep by Hypnotic Suggestion[2]

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DISCLOSURE STATEMENT: This was not an industry supported study. Financial support was from a Grant of the Swiss National Foundation (SNF) (PP00P1_133685) and the Clinical Research Priority Program (CRPP) “Sleep and Health” of the University of Zurich. The work was performed at the University of Zurich, Institute of Psychology, Department of Biopsychology, Zurich, Switzerland. The authors have indicated no financial conflicts of interest.

Short title: Hypnotic Suggestions Deepen Sleep

Submitted for publication July, 2013
Submitted in final revised form February, 2014
Accepted for publication February, 2014

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Acknowledgments: We thank Sandra Perner, Isabelle Braham, Sarah Schoch, Benjamin Roth, Mirjam Stieger, Melissa Maeder, Andrea Schmidt for assistance in data collection and Sandra Ackermann for helpful comments. This work was supported by a Grant of the Swiss National Foundation (SNF) (PP00P1_133685) and the Clinical Research Priority Program “Sleep and Health” of the University of Zurich.

Abbreviations: SWS: Slow-wave sleep; SWA: Slow-wave activity; EEG: Electroencephalography; REM: Rapid eye movement; EMG: Electromyogram; ECG: Electrocardiogram

[2] A similar version of this manuscript has been published in „SLEEP“

Abstract

Study Objectives: Slow-wave sleep (SWS) plays a critical role in body restoration and promotes brain plasticity; however, it markedly declines across the lifespan. Despite its importance, effective tools to increase SWS are rare. Here we tested whether a hypnotic suggestion to “sleep deeper” extends the amount of SWS.

Design: Within-subject, placebo-controlled crossover design.

Setting: Sleep laboratory at the University of Zurich, Switzerland.

Participants: Seventy healthy females 23.27 ± 3.17 y.

Intervention: Participants listened to an auditory text with hypnotic suggestions or a control tape before napping for 90 min while high-density electroencephalography was recorded.

Measurements and Results: After participants listened to the hypnotic suggestion to “sleep deeper” subsequent SWS was increased by 81% and time spent awake was reduced by 67% (with the amount of SWS or wake in the control condition set to 100%). Other sleep stages remained unaffected. Additionally, slow-wave activity was significantly enhanced after hypnotic suggestions. During the hypnotic tape, parietal theta power increases predicted the hypnosis-induced extension of SWS. Additional experiments confirmed that the beneficial effect of hypnotic suggestions on SWS was specific to the hypnotic suggestion and did not occur in low suggestible participants.

Conclusions: Our results demonstrate the effectiveness of hypnotic suggestions to specifically increase the amount and duration of SWS in a midday nap using objective measures of sleep in young, healthy, suggestible females. Hypnotic suggestions might be a successful tool with a lower risk of adverse side effects than pharmacological treatments to extend SWS also in clinical and elderly populations.

Keywords

high-density EEG, hypnosis, sleep, slow-wave sleep

Citation

Cordi MJ, Schlarb AA, Rasch B. Deepening sleep by hypnotic suggestion. SLEEP 2014;37(6):1143-1152.

Introduction

Sleep disturbances are highly common and present a major challenge for modern societies. Disturbed and insufficient sleep is strongly associated with several major diseases including hypertension, cardiovascular disease, obesity, depression, anxiety, bipolar disorders, and Alzheimer's disease (Aydin et al., 2013; Gangwisch, Feskanich, Malaspina, Shen, & Forman, 2013; Ju, 2013; Newman, Enright, Manolio, Haponik, & Wahl, 1997; Ohayon & Vecchierini, 2005; Vorona et al., 2005). In particular, slow-wave sleep (SWS) has proven vital for health and well-being, and slow-wave activity (SWA) during SWS benefits both the immune system as well as cognitive functions and brain plasticity (Anderson & Horne, 2003; Bryant, Trinder, & Curtis, 2004; Lange, Dimitrov, & Born, 2010; Rasch & Born, 2013; Tononi & Cirelli, 2006). Importantly, both the amount of SWS and SWA are strongly reduced across the lifespan, and the reduction in SWS has been linked to age-related prefrontal brain atrophy and memory impairments (Backhaus et al., 2007; Mander et al., 2013). Furthermore, frequently prescribed sleep-inducing drugs typically hinder the occurrence of SWS, lose their efficacy during long-term treatment, have adverse side effects, and often are associated with a high risk of addiction (Hajak & Rüther, 2006; Riemann & Perlis, 2009). Thus, the development of efficient and risk-free approaches to improve sleep and particularly SWS are highly warranted.

One non-pharmacological approach to improve sleep is hypnosis (Borkovec & Fowles, 1972; Schlarb, 2005; Stanton, 1989). Although there are different definitions of hypnosis, Oakley and Halligan (2009) define hypnosis as a state of changed mental activity after an induction procedure that mainly encompasses a state of focused attention and absorption. Importantly, during the state of hypnosis, suggestible subjects respond more easily to hypnotic suggestions, which are statements given during induction or afterward, intended to change or influence behavior. They can include decrease of pain, motor paralysis, or posthypnotic amnesia, and recent cognitive neuroscience research has successfully demonstrated effects of these suggestions on underlying brain activation using objective neuroimaging methods (Bell, Oakley, Halligan, & Deeley, 2011; Cojan et al., 2009; Cojan, Archimi, Cheseaux, Waber, & Vuilleumier, 2013; Kihlstrom, 2013; Mendelsohn, Chalamish, Solomonovich, & Dudai, 2008; Posner & Rothbart, 2011). In therapeutical contexts, hypnosis has been proven an effective tool in reducing pain, anxiety, and stress-related disorders (Bongartz, Flammer, & Schwonke, 2002; Flammer & Bongartz, 2003) and several studies provide evidence for a beneficial effect of hypnosis on sleep disturbances and insomnias (Borkovec & Fowles, 1972; Schlarb, 2005; Stanton, 1989). However, most of these studies are either case reports or include only subjective measures of sleep quality, whereas well-controlled experimental studies including objective sleep parameters and standard polysomnography are lacking (Schlarb & Gulewitsch, 2011). In particular, no study has ever tested whether hypnotic suggestions are effective in increasing

objective measures of sleep, like the amount of SWS or SWA. And finally, the possibility to induce SWS by hypnotic suggestions would be highly relevant in clinical terms as well as for healthy aging.

Here we tested whether a hypnotic suggestion to "sleep deeper" increases the amount of SWS and SWA using high-density electroencephalographic (EEG) recordings in a sleep laboratory (experiment 1). We show that the hypnotic suggestion increases the amount of SWS and SWA during a midday nap in healthy, non-habitual nappers suggestible to hypnosis compared to a non-hypnotic control text. Two additional groups of suggestible females assured that the effects of the hypnotic agent were not purely the result of mere expectancy effects (experiment 2) or demand characteristics of the experiment (experiment 3). Furthermore, we observed no beneficial effects of the hypnotic suggestion on subsequent SWS in two groups of low suggestible participants who either normally listened to the hypnotic suggestion (experiment 4) or tried to simulate the effects of the hypnotic suggestion on subsequent sleep (experiment 5).

Methods

Participants

A total of 70 healthy, German-speaking young females with a mean age (± standard deviation [SD]) of 23.27 ± 3.17 y (age range 18-35 y) took part in the five experiments. Only females were recruited to avoid gender effects. Suggestibility to hypnosis was verified by the Harvard Group Scale of Hypnotic Susceptibility (HGSHS) prior to the experiment (cutoff score for high suggestibility: HGSHS ≥ 7) (Bongartz, 1985). Fourteen highly suggestible (HGSHS: 7.61 ± 0.2) females (mean age 23.36 ± 2.7 y) participated in the main (first) experiment. In experiments 2 and 3, 14 highly suggestible females (mean age 23.71 ± 3.0 y; HGSHS: 7.73 ± 0.2) and 12 highly suggestible females (mean age 23.92 ± 4.60 y, HGSHS: 7.09 ± 0.08) were included, respectively. In experiments 4 and 5, 15 low suggestible females (mean age 23.47 ± 3.0 y; HGSHS: 5.07 ± 0.3) and 12 low suggestible subjects (mean age 22.25 ± 2.60 y; HGSHS: 5.24 ± 0.25) participated. Three subjects were excluded due to sleep diaries indicating irregular sleep times or regular afternoon naps. Age did not differ between the five experimental groups ($P > 0.70$). None of the participants had shift work within the prior 6 w, nor a history of neurological or psychiatric disorders. Participants reported normal sleep (Pittsburgh Sleep Quality Index (PSQI) < 6, (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989)), did not take any sleep influencing medication, did not regularly have an after-lunch nap, and were asked to refrain from caffeine and alcohol during the test day. Participants gave their written consent to take part in the study and were paid 140 Swiss francs for participation. The ethics committee of the University of Zurich approved the study.

Procedure

All participants had an adaptation nap and two experimental nap sessions in the sleep laboratory. The experimental sessions took place on the same day of the week, spaced exactly 7 days apart. One week before each of the experimental sessions, subjects started filling out a sleep diary. Except those from experiment 3, all subjects in all experimental groups were explicitly informed about the study purpose to deepen their sleep with the help of hypnosis. The experimental sessions started at 01:00 with attachment of 128 EEG electrodes, electromyographic (EMG), and electrocardiographic (ECG) electrodes for recording while listening to the text and subsequent napping. When participants were lying in bed, lights were turned off and the tape recording was started. Participants listened either to the tape including hypnotic suggestions or the control tape played over bedside speakers, in a randomized and balanced order. The duration of the tape recordings was 13 min. Participants were allowed to fall asleep during or directly after the record, and were, in all conditions, awakened after 90 min in bed (see Figure 1 for a summary of the procedure). After awakening, participants filled out a subjective sleep quality questionnaire (Görtelmeyer, 2011). Before going to bed, participants performed a declarative (word pairs) (Rasch, Born, & Gais, 2006) and a procedural memory task (sequence finger tapping) (Walker, Brakefield, Hobson, & Stickgold, 2003), which they recalled after the nap. Parallel versions were used in a randomized order (see supporting information and Table S1 for details). At the end of the second experimental session, participants filled out a general postexperimental questionnaire.

Experimental Design

A total of five separate experiments were conducted. Each experiment contained a within-subject comparison of two experimental naps according to a placebo-controlled crossover design. In the main experiment (experiment 1), participants suggestible to hypnosis (HS) either listened to a tape containing hypnotic suggestions to “sleep deeper” or a control text. The hypnotic tape contained a standard hypnotic induction section followed by a hypnotic suggestion section (i.e., a metaphor of a fish swimming deeper and deeper into the water). The control text contained a neutral documentation on mineral deposits. While the hypnotic text was spoken in a soft, slow, hypnotic, calming voice, frequently containing relaxing words such as “deep” “easily”, “relax”, “let go”, the control text was spoken in a normal voice and normal speed containing neither relaxing nor arousing words (see supporting material for further details on the texts). In experiment 2, highly suggestible participants also listened to a hypnotic and a control tape, but the hypnotic tape was altered now suggesting to “sleep shallower” (i.e., a metaphor of a boat resting on the surface). Importantly, the hypnotic induction procedure, the voice, the slow-relaxing way of speaking and the

inclusion of relaxing words was identical to the hypnotic tape used in experiment 1. In experiment 3 (demand characteristics), no hypnotic induction procedure or hypnotic suggestions were used. Here, suggestible participants were simply informed that listening to verbal information before sleep increases subsequent SWS as the brain tries to consolidate the learned information. The tape on mineral deposits (used as control tapes in all other experiments) was used to "induce" SWS in this experiment, and an incomprehensible version of the text was used as control condition. In experiments 4 and 5, low suggestible participants (LS) listened to identical hypnotic and control tapes used in the main experiment (experiment 1). The procedure and instructions in experiment 4 were identical to experiment 1. In experiment 5, low suggestible participants were asked to simulate the effects of the hypnotic suggestion. All tape recordings used in the different experiments were spoken by the same male voice (B.R., see supporting material for details on the tape recordings).

Figure 1. Experimental Procedure

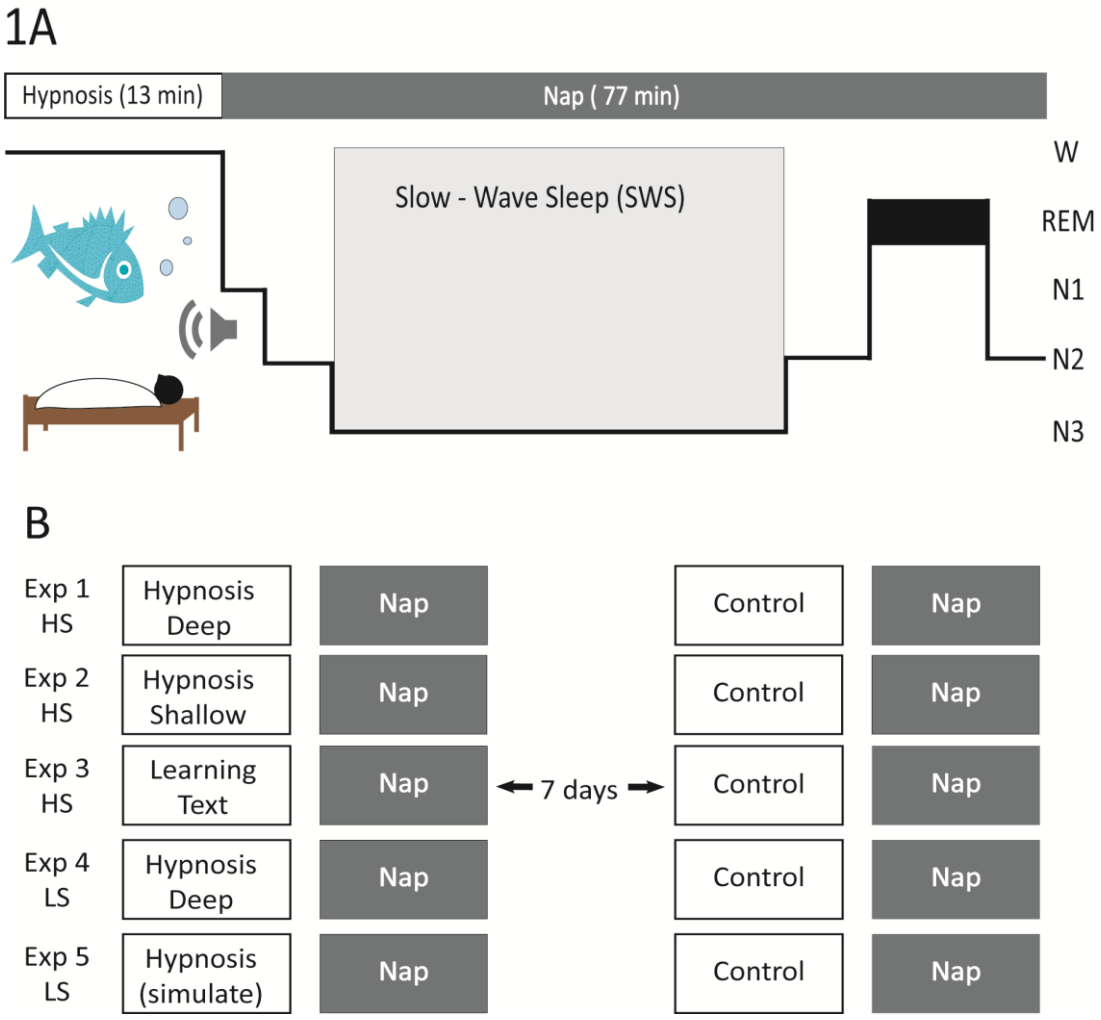

Figure 1. Overview of the experimental procedure. (A) Healthy young females listened either to a tape with hypnotic suggestions or a control tape while lying in bed, and were allowed to fall asleep afterward. The hypnosis tape included a standardized induction procedure, followed by a specifically developed metaphor of a fish swimming deep into the sea, repeatedly containing the suggestion to "sleep deeper" (see supporting information, for a more detailed description). The control text had the same length and consisted of a documentation of natural mineral deposits. (B) All subjects participated in a hypnosis and a control condition, separated by one week. In the main experiment (experiment 1), participants suggestible to hypnosis (HS) listened to the hypnotic suggestion "to sleep deeper" (i.e., the fish). In experiment 2, only the hypnotic suggestion was altered now suggesting "to sleep shallower" (i.e., a boat, resting on the surface). In experiment 3 (demand characteristics), suggestible participants were informed that listening to verbal information before sleep increases subsequent slow-wave sleep as the brain tries to consolidate the learned information. An incomprehensible version of the text was used as control condition. In experiment 4, low suggestible participants (LS) listened to the suggestion "to sleep deeper". In experiment 5, LS participants were asked to simulate the effects of the hypnotic suggestion. In the control condition, all participants listened to the same neutral text (except in experiment 3).

Statistical Analyses

Sleep was scored by two experts blind to experimental condition and analyzed using a repeated- measures analysis of variance (ANOVA) using the repeated factor "text" (hypnosis versus control) and the between subject factor "experiment" (experiment 1 versus experiment 2, experiment 1 versus experiment 3; experiment 1 versus experiment.4; experiment 4 versus experiment 5, respectively). For identification of sleep stage specificity, the repeated factor "sleep stage" was included. For EEG power analyses, the repeated factor "topography" (frontal, central, parietal) was used. Significant main effects and interactions were further explored using paired sample t-tests. Associations were explored with Pearson correlations. The level of significance was set to P = 0.05. In case variance homogeneity was not fulfilled, values were Greenhouse-Geisser corrected.

Results

Influence of the Hypnotic Suggestion on Subsequent SWS in Suggestible Females (Experiment 1)

As predicted, the hypnotic suggestion to "sleep deeper" strongly increased the amount of SWS during the subsequent nap. After listening to the text with hypnotic suggestions, participants showed an SWS amount of 181.2 ± 28.95% (mean ± standard error of the mean [*SEM*]), with percentage of SWS after the control text set to 100%. Thus, participants almost doubled their amount of SWS during the nap after the hypnotic suggestion compared to the control condition, indicating a very strong influence of the hypnotic suggestion to sleep deeper on later SWS amounts. This increase in SWS by hypnotic suggestions was statistically significant ($t(13) = 2.90$, P = 0.013, *Cohen's d* = 0.77 see Figure 2A). In addition to successfully increasing SWS, the influence of the hypnotic suggestion was highly specific: although the SWS percentage of total sleep time increased from 16.89 ± 4.38% after the control text to 30.60 ± 4.89% after hypnotic suggestions, we observed no changes in the percentages of sleep stages N1, N2, or rapid eye movement (REM) sleep after hypnotic suggestions compared to the control condition (all P > 0.40, see Figure 2B; see Table S2 for descriptive values). Additionally, the percentage of time awake after sleep onset was marginally reduced after hypnosis condition (7.34 ± 3.88%) as compared to the control condition (22.34 ± 7.60%; $t(13) = -2.02$, P = 0.065, $d = 0.54$). The sleep stage specificity of the influence of hypnotic suggestions on sleep architecture was confirmed by a significant interaction between the experimental condition (hypnosis versus control text) and sleep stage (W, N1, N2, SWS, REM; $F(2.0,$

26.06) = 3.73, P = 0.037, η^2 = 0.22). Total sleep time did not differ between experimental conditions (74.11 ±4.89 min versus 75.68 ± 4.86 min, respectively; P > 0.80).

Figure 2. Effects of Hypnotic Suggestions

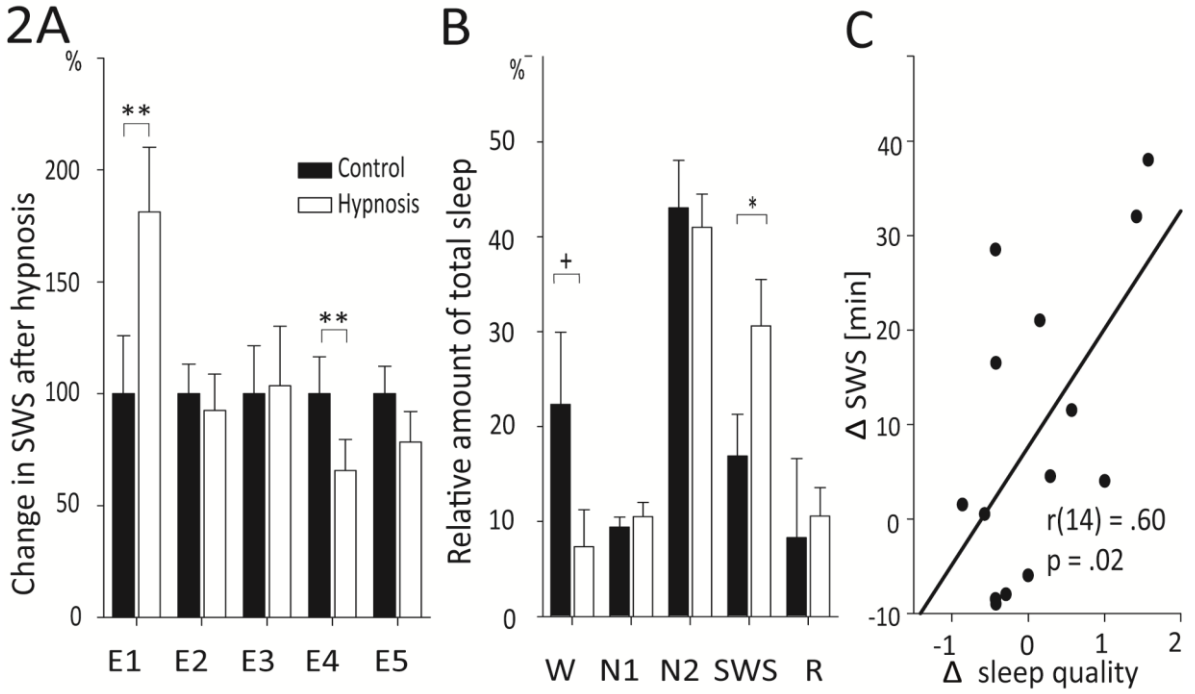

Figure 2. Effects of the hypnotic suggestions on sleep. (A) Highly suggestible subjects in experiment 1 almost doubled their amount of slow-wave sleep (SWS) after the hypnotic suggestion "to sleep deeper" (white bar), with the SWS amount after the control tape set to 100% (black bar). Using the suggestion "to sleep shallower" the beneficial effect of hypnotic suggestions on SWS in a group of highly suggestible subjects was completely abolished (experiment 2). Similarly in experiment 3, no increase of SWS was observed after listening to verbal information, even though participants were informed previously that listening to verbal information should increase subsequent SWS (demand characteristics). In low suggestible subjects, the suggestion "to sleep deeper" even decreased the amount of SWS (experiment 4), and the direction of the effect was similar when subjects were asked to simulate the effect of hypnotic suggestion on subsequent sleep (experiment 5). (B) The hypnotic suggestion "to sleep deeper" specifically increased the amount of SWS in experiment 1, whereas time awake after sleep onset (W) was marginally reduced, leaving the other sleep stages unaffected (N1/N2: nonrapid eye movement sleep stage 1 and 2, R,: rapid eye movement sleep). Means ± standard error of the mean are indicated. +: P ≤ 0.08; *: P ≤ 0.05; **: P ≤ 0.01; *** of P ≤ 0.001. (C). The hypnosis-induced increases in SWS significantly correlated with subjective increases in sleep quality in experiment 1.

Specificity of the Hypnotic Suggestion: Expectancy and Demand Characteristics (Experiments 2 and 3)

One might argue that the beneficial effect of hypnotic suggestion on SWS is actually because of a placebo effect caused by the expectancy or belief of the participants. Prior to the experiment, all participants were explicitly informed that hypnosis is effective and should result in deeper sleep, which might have deepened subsequent sleep independent of the hypnotic suggestion itself. To exclude this alternative, we recruited a second group of suggestible females, which also received the information that hypnosis will result in deeper sleep prior to the experiment. After the identical hypnotic induction procedure, however, the hypnotic suggestion was altered, now suggesting that the participants should sleep shallower (i.e., metaphor of a boat that rested on the surface of the sea; see supporting information). The results of experiment 2 clearly indicate that the subjective belief of the participants is not sufficient to induce SWS, and that the type of suggestion during hypnosis is critical: After listening to the hypnotic text suggesting sleeping shallower, participants exhibited a relative decrease in SWS amount (92.45 ± 16.19%) as compared to the control condition (set to 100%). However, this decrease was not statistically significant ($P > 0.60$, see Figure 2A). Other sleep stages were also not affected (all $P > 0.40$, see Table S2). A direct comparison between experiments 1 and 2 confirmed that SWS increases were only observed after the suggestion to "sleep deeper" (ANOVA experiment 1 versus 2 *hypnosis versus control text, $F(1, 26) = 5.70$, $P = 0.024$, $\eta^2 = 0.18$, see Table S2).

In addition, we attempted to exclude that the reported benefits of hypnotic suggestion on SWS are solely caused by demand characteristics of the experimental situation. We conducted a third experiment (experiment 3) with suggestible females, informing them that listening to verbal information before sleep increases subsequent SWS as the brain aims at consolidating this information during deep sleep. In a design identical to that of the two previous experiments, participants either listened to verbal information (i.e., the control text used in in experiments 1 and 2) and an incomprehensible version of the control text. Incomprehensibility was achieved by low-pass filtering the audio file of the control text, leaving the intonation and length of the text intact but rendering comprehension of the words impossible. All participants were informed that listening to the comprehensible version of the text before sleep should increase subsequent SWS, whereas listening to the incomprehensible version should not. Again, we did not observe any effect of the demand characteristics of the experimental situation on subsequent sleep. Participants in the "SWS-induction" condition exhibited 103.59 ± 26.55% SWS, with the amount of SWS in the incomprehensible text condition set to 100% ($P > 0.80$). In addition, no other sleep parameters differed between the two conditions (all $P > 0.15$). Directly comparing induced changes in SWS between experiment 1 and experiment 3 confirmed that an increase in SWS required listening to an

audio file with a hypnotic suggestion (ANOVA experiment 1 versus 3 * hypnosis versus control text, $F(1, 24) = 4.31$, $P = 0.049$, $\eta^2 = 0.15$, see Table S2 for descriptive values), safely excluding that the beneficial effects of hypnotic suggestion on SWS are due to demand characteristics of the experimental situation.

No Beneficial Effects of the Hypnotic Suggestion in Low Suggestible Females (Experiments 4 and 5)

Because the first three experiments only included participants with high hypnotic suggestibility, in experiments 4 and 5 we tested whether a hypnotic suggestion to sleep deeper is also effective in participants who exhibit low hypnotic suggestibility. The experimental procedure was identical to experiment 1, including the hypnotic suggestion to "sleep deeper". In experiment 4, the instructions to listen to the tape with the hypnotic suggestion were identical those in experiment 1. In experiment 5, low suggestible females were asked to 'simulate' the effects of the hypnotic suggestion on subsequent sleep. In contrast to highly suggestible subjects, low suggestible subjects in experiment 4 did not exhibit an increase in SWS during the nap after listening to the hypnotic text. In fact, the amount of SWS decreased to 65.70 ± 13.77% in the hypnosis condition, with the amount of SWS in the control condition set to 100% ($t(14) = -3.26$, $P = 0.006$, $d = 0.84$; see Figure 2A). Again, the effect was specific to SWS, as no other sleep stage was significantly altered in the hypnosis as compared to the control condition (all $P > 0.30$, see Table S3 for descriptive values). A direct comparison between experiments 1 and 4 confirmed that high suggestibility is substantial for the beneficial effect of hypnotic suggestions on SWS (ANOVA experiment 1 and experiment 4 * hypnosis versus control text, $F(1, 27) = 18.02$, $P \leq 0.001$, $\eta^2 = 0.40$, see Tables S2 and S3). These results also held when the single participant who did not fall asleep during both sessions was excluded from analyses.

Also in experiment 5, we observed no beneficial effects of the hypnotic suggestion, even though low suggestible females were asked to 'simulate' the effects of the hypnotic suggestions on subsequent sleep. As in experiment 4, the amount of SWS was decreased in the hypnosis condition (78.29 ± 13.73%, with the amount of SWS in the control condition set to 100%), although the difference did not reach significance ($P > 0.30$). No other sleep parameters significantly differed between the conditions (all $P > 0.08$), except a reduction in REM sleep after simulation of the effects of the hypnotic suggestion ($P = 0.02$, see Table S3 for descriptive values). A direct comparison between experiments 1 and 5 with respect to the changes in SWS confirmed that even simulation of high suggestibility is not sufficient to achieve beneficial effects of an hypnotic suggestion on subsequent SWS (ANOVA experiment 1 and experiment 5 * hypnosis versus control text, $F(1, 24) = 5.89$, $P = 0.023$, $\eta^2 = 0.20$, see Tables S2 and S3). Interestingly, combining the results of the effects of

the hypnotic suggestion to sleep deeper in low suggestible females (experiments 4 and 5) revealed a significant main effect of the type of text (hypnosis versus control), indicating a significant decrease in SWS after listening to the hypnotic suggestion in experiments 4 and 5 ($F(1, 25) = 5.10$, $P = 0.033$, $\eta^2 = 0.17$), but no interaction ($P > 0.70$).Thus, subjects with low suggestibility might possibly even actively counteract the beneficial effects of hypnotic suggestions on sleep architecture, whether they are listening normally to the hypnotic suggestion or trying to 'simulate' its effects.

Analysis of Control Variables (Experiments 1-5)

To exclude the possibility that the different results of the five experimental groups are in fact caused by differences in falling asleep during the listening period, we compared average sleep latency between groups and conditions. However, sleep latency was on average larger than the duration of the audio tape (13 min) and did neither differ between experiments ($P > 0.60$) nor between conditions (15.18 ± 4.06 versus 15.29 ± 3.70 min, $P > 0.90$; 14.93 ± 2.60 versus 20.18 ± 4.12 min, $P > 0.20$; 19.92 ± 8.56 versus 9.54 ± 2.20 min, $P > 0.20$; 14.70 ± 6.07 versus 16.37 ± 6.34 min, $P > 0.60$; 9.88 ± 2.31 versus 7.63 ± 1.85 min, $P > 0.30$; for experiments 1-5, hypnosis versus control, respectively). While listening to audio tapes, subjects neither differed in min spent in N1 between text conditions (3.18 ± 0.6 versus 2.21 ± 0.5 min, $P > 0.20$; 2.64 ± 0.67 versus 2.18 ± 0.76 min, $P > 0.40$; 2.21 ± 0.72 versus 1.96 ± 0.49, $P > 0.70$; 2.93 ± 0.75 versus 2.6 ± 0.50, $P > 0.70$; 1.92 ± 0.55 versus 2.00 ± 0.36, $P > 0.90$; for experiments 1-5, hypnosis versus control, respectively) nor was there a difference between experiments 1-5 ($P > 0.60$). Moreover, most subjects indicated that they had listened to the audio tapes, particularly when the hypnotic suggestions were given (see Table S4).

We also analyzed whether the changes in SWS in the five experimental groups resulted in differences in subjective sleep quality. Despite the robust increases in SWS in experiment 1, these changes were not reflected in averaged subjectively rated sleep quality (3.45 ± 0.18 versus 3.34 ± 0.20; in hypnosis and control condition, respectively, $P > 0.50$). However, on the individual level, differences in the duration of SWS between the hypnosis and control session reliably predicted differences in subjective sleep quality between the hypnosis and control session ($r(12) = 0.60$, $P = 0.023$, see Figure 2C). Participants in experiments 2-5 did not indicate any changes in sleep quality (3.58 ± 0.19 versus 3.68 ± 0.16; 3.37 ± 0.24 versus 3.11 ± 0.22; 3.46 ± 0.26 versus 3.45 ± 0.31; 3.21 ± 0.35 versus. 3.64 ± 0.20, all $P > 0.20$).

In addition, we analyzed whether the differences in amounts of SWS resulted in differences in memory consolidation across sleep. Although consolidation of declarative memories has been previously suggested to depend on SWS, we did not see any significant changes in consolidation measures across the nap between the hypnosis and the control condition in experiment 1 (102.92 ± 3.34% versus 100.41 ± 1.30% remembered word pairs, with learning performance before sleep set to

100%, P > 0.40). Likewise, consolidation in the procedural finger-tapping task did not differ between the hypnosis and the control condition (118.82 ± 6.14% versus 114.23 ± 4.14% correctly tapped sequences, with learning performance before sleep set to 100%, P > 0.40). Similarly, no condition effects on changes in memory performance were observed for declarative and procedural memory consolidation in experiments 2-5 (all P > 0.30, see Table S5). The order in which the parallel versions were presented had no influence in none of the experiments (all P > 0.20).

Finally, additional analyses confirmed for experimental groups 1, 2, and 4 that hypnotic suggestions did neither influence the proportion of subjects reaching REM sleep (see Table S6), nor the number of nonrapid eye movement (NREM) sleep cycles (see Table S7) nor spindle density or sigma power (see Table S8).

Influence of the Hypnotic Suggestion on SWA During Sleep (Experiments 1, 2, and 4)

To further specify the effect of the hypnotic suggestion on objective sleep parameters, we calculated spectral power values for SWA (0.5-4.5 Hz) during NREM sleep. We focused on experiments 1, 2, and 4 because only in these three experiments was a real (and not simulated) hypnotic suggestion used. After suggesting sleeping deeper in experiment 1, we observed a widespread increase in SWA that was most pronounced in central and parietal regions (Figure 3, A and B, see Figure 3, C for an illustrated power spectrum). Statistical analysis with grouped electrodes in six topographical regions (left/right frontal, central, and parietal, respectively, see supporting methods and Figure S1) revealed a significant main effect of type of text (hypnosis versus control, $F(1, 13) = 5.67$, P = 0.03, $\eta^2 = 0.30$) and a significant interaction between type of text (hypnosis versus control) and topography (frontal, central, parietal) ($F(1.14, 14.8) = 5.48$, P = 0.03, $\eta^2 = 0.30$, Greenhouse-Geisser corrected, see Figure 3, D for *post hoc* contrasts). The overall increase in SWA after hypnotic suggestions in all electrodes was strongly correlated with the increase in time spent in SWS ($r(14) = 0.88$, P < 0.001, see Table S9). In addition to the significant interaction, a main effect of topography (frontal, central parietal, $F(1.22, 15.9) = 90.50$, P < 0.001, $\eta^2 = 0.87$, Greenhouse-Geisser corrected) occurred, revealing the well-known SWA distribution of higher SWA in frontal as compared to central and parietal regions in young adults. The same ANOVA for experiment 2 and experiment 4 did not reveal any differences in SWA between the hypnosis and control conditions (all P > 0.12).

Figure 3. Effects on SWA

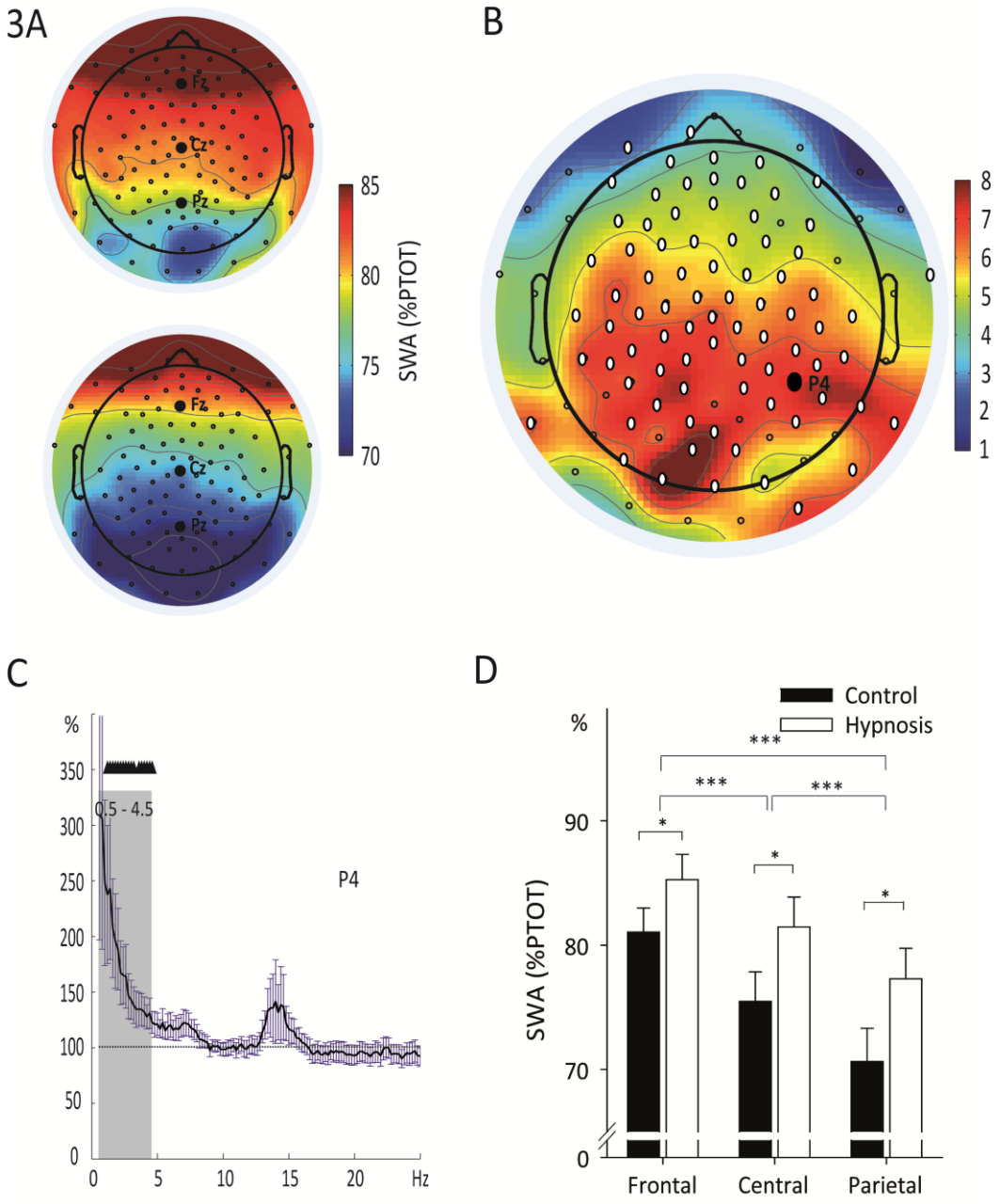

Figure 3. Changes in slow-wave activity (SWA) after hypnosis and control conditions in experiment 1. (A) Topographical distribution of SWA (0.5–4.5Hz) during nonrapid eye movement (NREM) sleep after listening to the hypnotic suggestion (upper panel) and the control text (lower panel). SWA is indicated as percent of total power (% PTOT; 0.5–50 Hz). Black dots represent electrode positions of the 128-channel electroencephalography (EEG) cap. (B) Topographical distribution of the difference of SWA %PTOT between hypnosis and control condition. White dots represent significant differences between the conditions, indicating a widespread increase in SWA during NREM sleep after the hypnotic suggestion "to sleep deeper". (C) Representative spectrogram of electrode P4. Black triangles indicate significant increases ($P < 0.05$) in SWA after hypnosis as compared to the control condition, which are highly specific for SWA (gray area). Mean increases ± standard error of the mean (SEM) are indicated for the hypnosis condition, with the control condition set to 100% (dotted line). (D) Averaged SWA over three topographical regions (frontal, central, parietal, see supporting information), for the hypnosis and control conditions. SWA is significantly increased after hypnosis as

compared to the control condition ($P < 0.03$), and the effect is stronger over central and parietal as compared to frontal regions (interaction type of text * topography: $P = 0.03$). Means ± SEM are indicated. *: $P \leq 0.05$; *** of $P \leq 0.001$, for *post hoc* contrasts.

Influence of the Hypnotic Suggestion on Theta Activity During Listening (Experiments 1, 2, and 4)

In addition to the effects of hypnotic suggestion on SWA during NREM sleep, we tested whether hypnosis induced changes in theta activity (4.5–8 Hz) during listening to the hypnotic suggestion. Again we focused on experiments 1, 2, and 4 because only in these three experiments was a real (and not simulated) hypnotic suggestion used. We specifically focused on theta activity because hypnotic trance states are typically associated with a general slowing of the EEG from alpha to theta frequencies (Crawford & Gruzelier, 1992; Sabourin, Cutcomb, Crawford, & Pribram, 1990). In addition, increases in theta activity are related to feelings of drowsiness and falling asleep (Schacter, 1977). As expected, suggestible participants in experiment 1 exhibited a significant increase in theta activity during listening to the suggestion part of the hypnosis text, as compared to an identical time period of the control text (13.46 ± 2.16% versus 11.05 ± 1.82%, main effect "text type" $F(1, 13) = 8.39$, $P = 0.013$, $\eta^2 = 0.39$, see Figure 4, A, B, and C). Generally, theta activity was higher in parietal (13.07 ± 2.17%) and central (13.25 ± 2.16%) as compared to frontal recording sites (10.44 ± 1.63%, main effect "topography" $F(1.37, 17.84) = 8.94$, $P = 0.004$, $\eta^2 = 0.41$, Greenhouse-Geisser corrected), whereas no significant interaction between text-type and topography occurred ($P > 0.40$). No differences in theta activity during listening to the hypnotic suggestion were observed in the other experiments ($P > 0.40$) (see Tables S2 and S3). Remarkably, the increase in theta activity in parietal regions during listening to the hypnotic suggestions as compared to the control text reliably predicted the increase in subsequent SWS duration ($r(12) = 0.60$, $P = 0.023$, See Figure 4, D and Table S9) and almost reached significance with respect to the overall increase in SWA ($r(12) = 0.51$, $P = 0.06$), suggesting a strong association between the immediate effects of the hypnotic suggestions during listening as indicated by theta activity and its later effects on SWS duration.

Figure 4. Activity during Listening to Hypnotic Suggestions

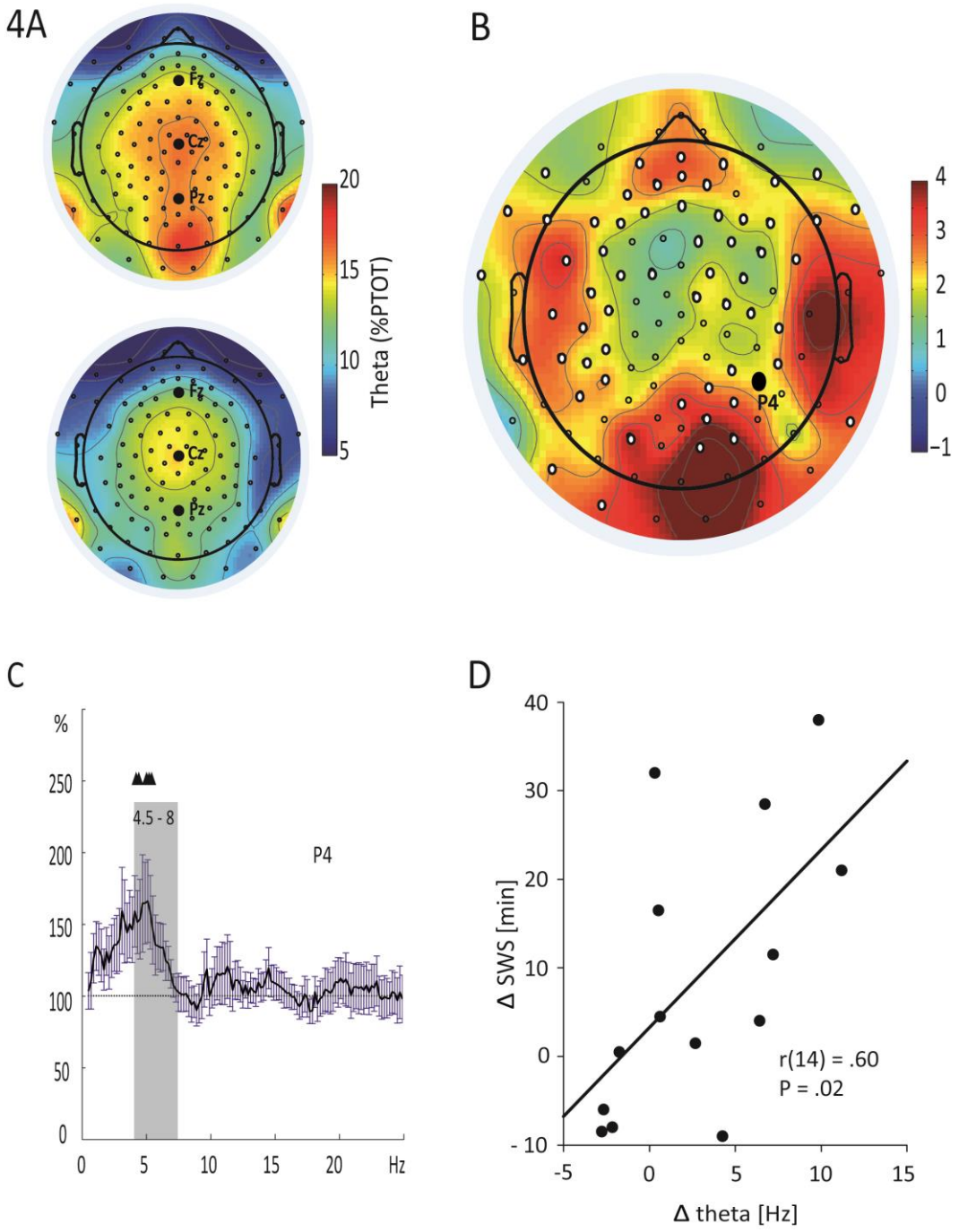

Figure 4. Theta activity during listening to the hypnosis versus the control text before sleep. (A) Topographical distribution of theta activity (4.5–8.0 Hz) during listening to the hypnotic suggestion (upper panel) and the control text (lower panel). Theta power is indicated as percent of total power (% PTOT; 0.5 - 50 Hz). Black dots represent electrode positions of the 128-channel electroencephalography (EEG) cap. (B) Topographical distribution of the difference of theta % PTOT between the hypnosis and the control condition. White dots represent significant differences between the conditions ($P < 0.05$), indicating a widespread increase in theta power during listening to the hypnotic suggestion "to sleep deeper". (C) Representative spectrogram of electrode P4. Black triangles indicate significant increases ($P < 0.05$) in theta power during listening to the hypnosis as compared to the control text, which occur mainly in the lower theta band (gray area). Mean

increases ± standard error of the mean are indicated for the hypnosis condition, with the control condition set to 100% (dotted line). (D) Increases in parietal theta activity during listening to the text with hypnotic suggestions as compared to the control text are highly predictive for subsequent changes in slow-wave sleep duration between the experimental conditions.

Discussion

Our results show for the first time that a hypnotic suggestion to "sleep deeper" selectively extends the amount of SWS in suggestible females. In addition, control experiments indicate that the suggestion during hypnosis is essential and that the effect does not occur in low suggestible participants. Furthermore, hypnotic suggestions induce an increase in SWA during subsequent NREM sleep and increases in theta activity during listening to audio tapes with hypnotic suggestions predict subsequent increases in SWS.

Our finding that a hypnotic suggestion before sleep increases the amount of SWS is highly relevant because SWS plays a critical role in the optimal functioning of our immune system (Lange et al., 2010), metabolism (Benedict et al., 2011), and optimal brain functioning (Hobson, 2005) in particular with regard to memory consolidation and brain plasticity (Rasch & Born, 2013; Tononi & Cirelli, 2006). The National Heart, Lung, and Blood Institute has estimated that 50 to 70 million Americans suffer from a chronic disorder of sleep (National Heart, Lung, 2003), which has severe consequences on daytime functioning (Goldman et al., 2007) and is associated with morbidities including hypertension, cardiovascular disease, depression, and anxiety (Gangwisch et al., 2013; Newman et al., 1997). Importantly, sleep-inducing drugs usually hinder the occurrence of SWS, lose their efficacy during long-term treatment, and have a high risk of addiction and adverse side effects (Hajak & Rüther, 2006; Riemann & Perlis, 2009). Although our study sample was limited to healthy participants, our results strongly suggest that suggestions given during hypnosis might be an efficient tool to improve sleep and SWS, also with respect to sleep disturbances. Increasing SWS by hypnotic suggestion might also have a beneficial effect in primary insomnia, as a recent meta-analysis by Baglioni and colleagues showed that primary insomnia is associated with significant SWS reductions (Baglioni et al., 2013), although this was not consistently confirmed for patients with chronic insomnia. Furthermore, the increase in SWS by hypnotic suggestion reported here was even more pronounced than increases in SWS induced by pharmacological treatments as reported previously (Rasch et al., 2006). Previous studies have already provided evidence for a positive effect of hypnosis on different sorts of sleep disturbances (Borkovec & Fowles, 1972; Schlarb, 2005; Stanton, 1989), and concluded that hypnosis is an effective treatment option for insomnias (Hauri, Silber, & Boeve, 2007). However, most of the studies included only a small sample size (Ng & Lee, 2008) and used subjective measures of sleep such as questionnaires or sleep diaries (Schlarb, 2005; Stanton, 1989). Here we showed that a hypnotic suggestion is also effective in increasing objective measures of SWS using standard polysomnography and high-density EEG, and that the increase in SWS predicted individual improvements in subjective sleep quality. Comparable to negative influences of emotional or cognitive factors that can influence sleep as stress or rumination (Van Reeth et al., 2000), hypnosis

might represent a positive example thereof, maybe influencing SWS by a calming effect on the arousal system. Although our sample only consisted of females, limiting generalization of the results, the possibility to improve SWS might be also highly relevant for healthy aging, because aging is strongly associated with a reduction in the amount of SWS, and the possibility to use hypnotic suggestions to increase SWS could prove critical for maintaining optimal cognitive functioning and health in old age (Harand et al., 2012; Mander et al., 2013; Wilckens, Erickson, & Wheeler, 2012). Although, for instance, Ehrenreich (1949) reported a slight decline in hypnotizability score as a function of age, there is evidence that the elderly are as suggestible as young adults and robust test-retest correlations exist (Piccione, Hilgard, & Zimbardo, 1989). A limitation of our study is that we did not include an intervention-free control group or a control group not performing memory tests before sleep. Thus, we cannot completely rule out the possibility that listening to the control text or working on memory tests might also have affected the amount of SWS. However, amounts of SWS in other intervention-free nap studies using a comparable sample and design are close to the amount we observed in the control condition (i.e., 18.09% in the study by Mednick, Cai, Kanady, and Drummond (2008)) and hypnosis condition (i.e., 33.1% in the study by Hofer-Tinguely et al. (2005)), which suggests that the amount of SWS in our study varied within the normal range. Please note that we only included non-habitual nappers who might not sleep as deeply as subjects used to having midday naps.

Related to the increase in SWS, we also showed that the hypnotic suggestion induced a widespread increase in SWA during NREM sleep. SWA is a more precise quantitative measure of sleep depth, reflecting the reduction of sleep pressure across sleep and has been implicated in brain plasticity, synaptic downscaling, immune function, and memory consolidation (Besedovsky, Lange, & Born, 2012; Huber et al., 2006; Huber, Ghilardi, Massimini, & Tononi, 2004; Tononi & Cirelli, 2006). Local differences in SWA during sleep have been related to plastic changes in these brain regions (Huber et al., 2006, 2008, 2004). In particular, changes in SWA are associated with changes in prefrontal atrophy and memory consolidation in the elderly (Mander et al., 2013). In our study, increases in SWA were particularly strong in parietal brain areas, although significant increases were also observed over frontal and central brain regions. Note that we included the average of all NREM sleep episodes and did not analyze changes in SWA across NREM episodes or changes in slow oscillations slope. This limits the possibility to exclude that the SWS increase had resulted from mechanisms different from natural ones. Please note that our sleep scorers who were blind to the experimental condition did not report anything unusual with respect to SWS. Because we did not observe any improvement in memory functions in experiment 1, the benefits for cognitive functioning of the hypnosis -induced increase in SWS, however, remain to be determined, particularly considering that other studies observed an increase in memory performance in similar

tasks after enhancing SWA by oscillatory stimulation (Marshall, Helgadóttir, Mölle, & Born, 2006). Interestingly, however, Mednick et al. (2013) recently reported that pharmacologically enhancing SWS only benefit declarative memory consolidation when sleep spindle density was also increased. Here, we did not observe a concomitant increase in sleep spindles number and density or power in the sigma band, which might explain the lack of an effect on declarative memory consolidation.

In addition to the effects on SWS and SWA, we observed increases in theta activity during listening to the hypnotic audio tapes, which were predictive for the subsequent beneficial effect of hypnotic suggestions on the duration of SWS and SWA. Previous EEG studies on hypnosis have frequently reported a general slowing of the EEG and an increase in theta activity during brain states of hypnotic trance (Deivanayagi, Manivannan, & Fernandez, 2007; Sabourin et al., 1990). In addition, alpha activity (indicative for quiet resting with eyes closed) characteristically decreases at the onset of light sleep stages and feelings of drowsiness (Schacter, 1977). However, no differences in sleep latency occurred between our experimental conditions and we did not observe any differences in sleep stage N1 during listening, indicating that participants did not fall asleep earlier while listening to the hypnotic suggestions as compared to the control text. Thus, the increase in theta activity might be indeed indicative for processes related to the hypnosis, particularly because it predicted the later effects of the hypnotic suggestion, i.e., the increase in SWS and SWA. Please note that we did not include any questionnaire or behavioral test to ensure that subjects were in the hypnotic state during or after listening to the hypnotic text.

In recent years, interest in the mechanisms and effects of hypnosis as well as hypnotic suggestion is growing in neuroscience research (Halligan & Oakley, 2013; Oakley & Halligan, 2011). According to Oakley and Halligan (2009) these studies “illustrate the potential of hypnotic suggestion as a powerful cognitive tool to explore in a controlled way selective phenomena directly relevant to cognitive and clinical neuroscience.” (Hajak & Rüther, 2006, p. 269). Several recent studies have examined the underlying brain effects of hypnosis and hypnotic suggestion with respect to motor inhibition, hypnotic analgesia, the default mode network and posthypnotic amnesia (Cojan et al., 2009, 2013; Crawford, Knebel, & Vendemia, 1998; Deeley et al., 2012; Mendelsohn et al., 2008). In general, studies on the effects of hypnosis during wakefulness have the disadvantage that they need to safely exclude that participants do not just “simulate” and conform to the demands of the experiment or the experimenter (i.e., demand characteristics). In our study, the argument is not valid, as the effects of the hypnotic suggestion are observed after the hypnosis during sleep without waking consciousness using objective EEG parameters. Thus, effects of hypnotic suggestions on sleep might be an elegant way to examine aftereffects of posthypnotic suggestions.

Generally, it is well known that our thoughts and subjective beliefs can influence sleep. Stress and particularly rumination of negative thoughts diminish sleep quality and sleep efficiency

(Vandekerckhove & Cluydts, 2010; Vandekerckhove et al., 2011). In addition, the anticipation of a certain wake up time has consequences on sleep length that can be objectively measured, e.g., by earlier increase in cortisol during sleep (Born, Hansen, Marshall, Mölle, & Fehm, 1999). Thus, changing inappropriate beliefs concerning sleep is one major target in clinical approaches to treat sleep disturbances (Morin, Blais, & Savard, 2002). However, intentionally "wanting" to fall asleep is often counterproductive; therefore, paradoxical interventions are sometimes more helpful to induce sleep (Ascher & Efran, 1978; Ascher & Turner, 1979). Thus, inducing sleep or extending SWS under hypnosis might bypass the explicit and voluntary intention, inducing subsequent sleep effects on a more subconscious level, not involving willing decision processes. In particular, the effects of the hypnotic suggestion were highly specific in our study: The suggestion to "sleep deeper" specifically extended duration of SWS, leaving other sleep stages unaffected. It remains to be tested whether different hypnotic suggestions may be capable of changing other sleep stages such as REM sleep or N2 sleep, which we expect to be possible in case an adequate metaphor can be developed.

The specificity of the hypnotic suggestion was further confirmed by showing that the beneficial effects of the hypnotic tape disappeared with a changed hypnotic suggestion. Although the suggestion to sleep deeper effectively increased the duration of SWS, the suggestion to sleep "shallower" had no effect on SWS. As the participants in experiment 2 were also told prior to the experiment that the hypnotic suggestions should result in deeper sleep, the absence of the effects in this condition clearly shows that the previous belief of the participants is not sufficient to elicit SWS changes and that the type of the hypnotic suggestion during the hypnosis is critical for the beneficial effect. Despite this apparently controversial input, a postexperimental questionnaire indicated that subjects did not assume that the hypothesis was different from what we told them and that they were not irritated by the content of the tape. It seems that subjects do not question the content of the hypnotic suggestion so critically. One might argue that the suggestion to sleep "shallower" should have induced an increase in light sleep stages in the control experiment. However, although the type of suggestion is critical, it might still be possible that the participants' belief plays some role in the effectiveness of hypnotic suggestions and that the belief to "sleep deeper" might have weakened the effectiveness of the hypnotic suggestion to sleep "shallower". Importantly, the null result in experiment 2 also excludes that the effects of hypnotic suggestions on deep sleep are simply caused by unspecific differences between the hypnotic tape and the control tape. For example, the hypnotic tape was spoken in a slow, relaxing, and calming voice, whereas the control tape was spoken in a neutral voice at normal speed and contained neither relaxing nor arousing words. Because these unspecific differences in the "relaxing nature" between the tapes are identical in experiments 1 and 2, they cannot explain why a beneficial effect on SWS occurred solely in experiment 1. In an additional control group, we tested the pure effect of expectancy and examined

whether a neutral (not hypnotic) text will also increase deep sleep. SWS was not affected by this belief alone without being given hypnotic suggestions. Alternatively, it might simply be less effective to induce lighter sleep as compared to deeper sleep using a hypnotic suggestion.

Finally, our experiments 4 and 5 indicate that the effectiveness of the hypnotic suggestion depends on the suggestibility of the participants. People strongly vary in their responsiveness to hypnotic suggestions, and the degree to which suggestibility remains stable over time might be partly the result of genetic differences (Kirsch & Lynn, 1995; Piccione et al., 1989; Szekely et al., 2010). Moreover, high suggestibility is associated with openness to experience (Kihlstrom, 2013) and focused attentional abilities (Hoeft et al., 2012; Lichtenberg, Bachner-Melman, Ebstein, & Crawford, 2004), which might be related to the fact that suggestibility is highly predictive for the success or failure of effects of hypnotic suggestions (Ray, Keil, Mikuteit, Bongartz, & Elbert, 2002) and the inclusion of high versus low suggestible participants is common practice in experimental studies on hypnosis (Kirsch & Lynn, 1995; Piccione et al., 1989; Rasch et al., 2006; Szekely et al., 2010). Interestingly, in our study, not only did low suggestible participants fail to increase SWS after the hypnotic suggestion, but in fact spent less time in SWS after the text including hypnotic suggestions, both when they normally listened to the hypnotic suggestion as well as when they were asked to simulate the effects of the hypnotic suggestion. This negative subject effect has already been described in previous studies, indicating that low suggestible subjects tend to counteract the implications of the suggestion instead of only failing to responding to them (Jones & Spanos, 1982). A possible explanation is the definition of the context within which the hypnosis is presented. Changing the setting from a hypnosis session into a test of imagination increases the score in a consecutive hypnotizability test for low suggestible subjects (Spanos, Gabora, Jarrett, & Gwynn, 1989). Thus, for low suggestible subjects it might be advantageous to emphasize a relaxing instead of a hypnotic state for the extension of SWS to avoid negative effects. Of note, the inverse effect in low suggestible participants renders it very unlikely that simply the relaxing nature of the hypnotic tape (i.e., voice, intonation, words, etc.) as compared to the control text was responsible for the observed changes in SWS in experiment 1.

Limitations

Our study included a highly selective sample of healthy, young females, which limits the generalizability of our results. Furthermore, our study was designed as a nap study, and further studies should test the effectiveness of hypnotic suggestions on SWS during nighttime sleep. Moreover, future studies should include an intervention-free control condition without listening to any text before sleep and control groups without presleep memory tests. Additionally, further

studies should characterize the hypnosis -induced increases in SWA in more detail (e.g., slope analyses, changes in SWA across NREM episodes, etc.). Finally, further simulator studies are required to answer the important question whether the reported effects of hypnotic suggestions on deep sleep are specific to the state of hypnosis *per se*, or whether they might similarly occur with more unspecific procedures involving prior expectations (i.e., demand characteristics), suggestions without hypnosis, and relaxation.

In summary, we show that a hypnotic suggestion to sleep deeper is effective in extending subsequent SWS and SWA in healthy participants. Our results imply that hypnotic suggestions are an efficient tool to deepen sleep and strongly indicate that hypnotic suggestions might prove an efficient non-pharmacological tool with a lower risk of adverse side effects than pharmacological treatments to also deepen sleep in patients with sleep disturbances or in the elderly, thereby improving health and well-being.

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Supporting Material for: Deepening Sleep by Hypnotic Suggestion

Abbreviations: PVT: Psychomotor Vigilance Test; PAL: Word Pair Associate Learning Task; N1 and N2: Stage 1 and 2 sleep; SWS: Slow-wave sleep; REM: Rapid eye movement sleep; TST: Total sleep time; SWS latency: Slow-wave sleep latency

Supporting methods

1. Hypnosis and Control Texts

The hypnosis texts were written by A. Schlarb, a coauthor and professional hypnotherapist treating sleep problems and sleep disorders with hypnosis. All texts were spoken and recorded by B. Rasch. The hypnosis texts started with a 4-min progressive induction technique, including 10 steps while each step indicated a further step into relaxation, leading the listener into the state of hypnotic trance. In the main hypnotic text used in experiment 1, the induction was followed by a hypnotic suggestion to sleep deeper. More specifically, the auditors were invited to imagine a picture of a sea and to follow a fish swimming in the water, progressively swimming deeper and deeper. The picture of the swimming fish and the sea was used as a metaphor to symbolize the depth of sleep. In addition, it was suggested that swimming deeper and deeper is safe and without any risk. Finally, the fish arrived at the bottom of the sea, whereby the auditors were further induced to sleep deeply. The tape with hypnotic suggestions stopped here and did not bring the listener out of the hypnotic trance. Instead, subjects were invited to fall asleep at any time afterward. In total, duration of the tape was 13 min in which 932 words were spoken with a soft, slow, hypnotic, calming voice, frequently containing relaxing words such as “sleep deep” “easily”, “relax”, “let go”.

The control text was a documentation concerning natural mineral deposits taken from Wikipedia (http://de.wikipedia.org/wiki/Lagerstättenkunde) and was also spoken and recorded by B. Rasch. The control text was matched to the hypnotic texts with respect to length in minutes and volume. In this text, 1,712 words were spoken with an everyday intonation and speed. The text was not designed to contain relaxing or arousing words in particular, but be as neutral and objective as possible.

In the second hypnotic text used in experiment 2, the identical induction of hypnotic trance from experiment 1 spoken by B. Rasch was followed by a hypnotic suggestion to sleep shallower. More specifically, the auditor was invited to imagine a picture of a sea and to be on a ship swimming

on the surface of the sea. The picture of the ship on the surface was used as a metaphor to symbolize light and shallow sleep, and it was suggested that it is safer to rest on the surface and not to go deep under water. The recording sounded almost identical to the recording used in experiment 1, containing 967 words that were spoken with a soft, slow, hypnotic, and calming voice, frequently containing words such as “sleep shallow” “easily”, “relax”, “let go”. As in experiment 1, the tape with hypnotic suggestions ended without bringing the listener out of the hypnotic trance.

The audio files with hypnotic suggestions (deep and shallow) as well as the control text are accessible on our homepage:
http://www.psychologie.uzh.ch/fachrichtungen/allgpsy/biopsy/links.html

2. Assessment of Suggestibility

Prior to participation in the experiment, suggestibility was assessed for all candidates using the Harvard Group Scale of Hypnotic Susceptibility Test, Form A (HGSHS: A; (Shor & Orne, 1963), German translation (Bongartz, 1985)), which represents a widely used standard measure of hypnotic suggestibility on a scale from 0 to 12. Of the initially screened 112 females, 68 turned out to be low suggestible according to the classification proposed by Bongartz (Bongartz, 1985). In the literature, suggestibility is reported to be normally distributed into high (49%) and low (51%) suggestible subjects (Bongartz, 1985; Oakley & Halligan, 2013)and quite robust test-retest correlations are reported (Piccione, Hilgard, & Zimbardo, 1989). In experiments 1 and 2, only females with a suggestibility index from 7 to 12 were included (highly suggestible subjects), whereas females with a suggestibility of 0 to 6 were included in experiment 3 (low suggestible subjects). Mean suggestibility was significantly lower in experiment 3, $F(1, 41) = 83.58$, $P < 0.001$.

3. Behavioral Tasks

In the Psychomotor Vigilance Test (PVT), a millisecond counter was displayed at random intervals and subjects had to press the space bar on the keyboard as quickly as possible after it began to count upward. The achieved reaction time in ms was displayed thereafter for 1 sec. The test is highly sensitive to measure the effects of tiredness on vigilance (Dinges & Powell, 1985).

The Word Pair Associate Learning Task (PAL) consisted of 80 pairs of semantically related words that were taken from Rasch et al. (2006). Two randomized and parallel lists were constructed according to concreteness, imagery, meaningfulness, valence, and arousal ratings as well as association strength of the words (see Table S1 for the word lists). Word pairs (e.g., clock- church) were presented in black font on a white background with E-Prime on a computer screen. After a fixation cross, present for 500 ms, word pairs were presented sequentially for 1 sec per word,

separated by a blank interval of 200 ms. A blank interval of 500 ms preceded the next fixation cross. The order of the word pairs was at random. Subjects were asked to learn the association between the two words for later cued recall, meaning recall of the second word, when only the first one was presented. The order of words during recall did not correspond to the one during learning. Response time was not restricted and no feedback was given. Retrieval was tested immediately and after the nap while word pairs were presented in the same order during both recall phases. Memory performance was measured using the number of correctly recalled words at retrieval after napping relative to the correctly recalled words after the learning phase. As a consequence, values can exceed 100%.

In the Procedural Finger Sequence Tapping Task (Walker, Brakefield, Hobson, & Stickgold, 2003), subjects were asked to replicate a five-element finger sequence with their non-dominant hand on a keyboard as fast and as accurately as possible. Learning period contained nine 30-sec trials interrupted by 30-sec breaks during which the sequence did not change and was displayed during the whole trial. The recall period after the nap contained only three trials. Each subject randomly conducted each of two created number sequences (4-1-3-2-4 versus 4-2-3-1-4) in either of the experimental sessions. Feedback about the number of completed sequences and the error rate was given after each block. The average score of correct sequences during the final three blocks was taken as measure of procedural memory performance before sleep while recall performance after sleep was measured by the average score of correctly completed sequences of the entire three blocks that were presented. “Overnight” changes in speed (number of entered sequences) and percentage of error rate (amount of errors per correct sequence), were calculated in percent, with performance before sleep set to 100%.

4. Polysomnographic Recordings

Sleep was recorded with electromyographic (EMG), electrocardiographic (ECG), and 128 electroencephalographic (EEG) electrodes (Electrical Geodesics, Inc.) referenced against the Cz channel using a sampling rate of 500 Hz. Data were preprocessed with VisionAnalyzer 2.0 (Brain Products, Germany), filtered using a notch filter (50 Hz) and standard filter settings suggested by the American Academy of Sleep Medicine (AASM) (e.g., EEG 0.3–35 Hz (Iber, Ancoli-Israel, Chessonn, & Quan, 2007)) and referenced against the mastoids. Sleep was visually scored based on derivations F4, C4, O4, HEOG, VEOG, and EMG using 30-sec periods according to standard criteria of the AASM (Iber et al., 2007) by two sleep experts blind to condition. In case of disagreement, a third expert was consulted who was also blind to condition. Stages 1-3, rapid eye movement (REM) sleep, and wake after sleep onset (WASO) were scored.

5. Analysis of EEG Data

For a more fine-grained exploratory analysis of the effects of hypnotic suggestions on oscillatory brain activity, high-density EEG recordings were subjected to power spectral analysis. For the analysis of direct effects of the hypnosis or control text, data from the 13 min during tape listening was segmented into segments of 4,096 data points (≈ 8 sec) with an overlap of 409 between segments. For the analysis of the effect of hypnotic suggestions on sleep, only nonrapid eye movement (NREM) sleep segments of N2 and N3 were selected and similarly segmented in periods of 4,096 data points with an overlap of 409 between segments. Participants lacking NREM sleep were excluded from the analysis. In both analyses, movement artefacts were controlled by automatically removing segments during which EMG activity was above +/- 200 µV. A Hanning window (10%) was applied on each 4,096-point block of EEG data before calculating the power spectra using fast Fourier transform with a resolution of 0.2 Hz. Individual mean power was determined in the slow-wave band (0.5–4.5 Hz) averaged across all NREM sleep episodes and in the theta band (4.5–8.0Hz) during listening to the auditory tape. Data were normalized on the average total power between 0.5 and 50 Hz. SWA was defined as power density between 0.5–4.5 Hz during NREM sleep, theta activity as power in the 4.5–8 Hz range during listening to the texts.

For statistical analysis, six topographical regions were defined: right frontal (electrodes 1-5, 8-10, 14, 116-118, 124, 121- 123), left frontal (electrodes 12, 17, 19-26, 28, 32-34, 38), right central (electrodes 79, 80, 87, 93, 102 -106, 108-112, 114, 115), left central (electrodes 7, 13, 29-31, 35-37, 39 -42, 44-46, 54), right parietal (electrodes 76-78, 82-86, 89-92, 95 -98, 100, 101), and left parietal (electrodes 47, 50-53, 57-61, 64-67, 69-71, 74) (see supporting Figure S1). We used the within-subjects factors “topography” (frontal, central, parietal), “laterality” (left, right), and “text” (hypnosis versus control) separately in each experiment for the repeated-measures analysis of variance on slow-wave activity during NREM sleep and on theta activity during listening to the audio tape. In addition, we show results for a representative single electrode (electrode P4) for an analysis of the specificity of the effects on the power spectrum.

Supplemental Table S1. Parallel versions of the paired associate task involved words, balanced according to concreteness, imagery, arousal, meaningfulness, association strength, frequency in use, and word length (Rasch et al., 2006).

Version A		Version B	
Word1	**Word2**	**Word1**	**Word2**
CHANCE	BEGEGNUNG	TRINKSPRUCH	SPRICHWORT
PLAN	GROSSSTADT	CHAOS	STRUKTUR
ZEIT	URSPRUNG	SKLAVE	KÖNIG
ERDGES-CHOSS	DACHBODEN	KUGEL	QUADRAT
PROFIL	PHOTOGRAPHIE	STURM	WINDHAUCH
BESITZ	ANTEIL	RÜSTUNG	ANGRIFF
TÄUSCHUNG	ECHTHEIT	ANEKDOTE	WITZ
GEBÄUDE	HOTEL	BEDÜRFNIS	WERBUNG
APFEL	PFIRSICH	MANGEL	VERZICHT
TAT	ABSICHT	SCHAMGEFÜHL	KÖRPER
AUTO	PRESTIGE	RÜCKSCHRITT	VERGANGENHEIT
NORM	MORAL	INFORMATION	INHALT
DEFINITION	KONZEPT	NÄSSE	GEWITTER
SEGEN	SCHÖPFER	ERDE	STEIN
GEIST	FLASCHE	DEMOKRATIE	SYSTEM
FORDERUNG	GEHALT	BECHER	KAFFEE
MEINEID	EHRENHAFTIG-KEIT	STAUB	SAUBERKEIT
INDUSTRIE	BRANCHE	URHEBER	KAUSALITÄT
PUDDING	SÜSSIGKEITEN	FORM	KREIS
STOLZ	RUHM	FIGUR	BRETT
ZWIELICHT	UNTERWELT	VOGEL	KATZE
WOLLE	KLEIDUNG	BERUF	ANERKENNUNG
VERGLEICH	GLEICHNIS	BARGELD	WERT
ALKOHOL	OPIUM	PELZ	FUCHS
BEWEIS	TATSACHE	SPASS	FEIER
GESUNDHEIT	IMPFUNG	STERN	WEIHNACHTEN
PAPIER	BRIEF	BEGRIFF	BEDEUTUNG
GIFT	MORD	FÄHIGKEIT	VERANLAGUNG
JUNGE	MÄDCHEN	ZEITUNG	DRUCK
ARMUT	ELEND	PUPPE	KIND
VULKAN	EXPLOSION	STILLE	EINSAMKEIT
STUHL	SESSEL	LÖSUNG	PROBLEM
GEDÄCHTNIS	ELEFANT	ABSPRACHE	VERTRAG
RICHTER	GERECHTIGKEIT	SÄNGER	KÜNSTLER
GESCHREI	PANIK	NUTZEN	KOSTEN
HELDENMUT	TAPFERKEIT	MASCHINE	APPARAT
ANSICHT	MEINUNG	EINGEBUNG	IDEE
LARVE	RAUPE	EMPFEHLUNG	RAT
LEIDENSCHAFT	KUSS	GEHIRN	BEWUSSTSEIN

DAMPF	LOKOMOTIVE	GRUNDRECHT	VERFASSUNG
BETRAG	WECHSEL	FRAGE	EINWAND
THEORIE	AUSNAHME	HAUT	BLUT
AUFGABE	ERLEDIGUNG	KRITIK	ZWEIFEL
GESCHICHTE	ENTWICKLUNG	UHR	KIRCHE
DIENER	HALTUNG	SCHICKSAL	IRONIE
ERFORSCHUNG	PATENT	VERLUST	ABNAHME
FAHNE	EROBERUNG	KRITERIUM	AUSWAHL
DIAMANT	GOLD	BEGRÜSSUNG	FREUNDLICHKEIT
BETTLER	UNGLÜCK	NEFFE	GROSSMUTTER
BEGABUNG	VERERBUNG	HÄRTE	KRAFT
VERRAT	TREUE	TAL	WIESE
STIRN	KINN	SPRACHE	AKUSTIK
GEDICHT	LIEBE	KOMÖDIE	DRAMA
ANDEUTUNG	VERDACHT	GESPENST	ERSCHEINUNG
GRUPPE	VERSAMMLUNG	PRÜFUNG	MISSERFOLG
LAUNE	HUMOR	ERLÖSUNG	HIMMELREICH
GENUSS	ZIGARRE	ANFORDERUNG	SCHWIERIGKEIT
MERKMAL	DETAIL	MALER	PIANIST
BESESSENHEIT	TEUFEL	FASS	KELLER
LABYRINTH	SUCHE	AUSWERTUNG	ERGEBNIS
NAGEL	METALL	ZUWACHS	FORTSCHRITT
ANGST	SCHLANGE	ILLUSION	WAHRNEHMUNG
ANGEBOT	MARKT	TIER	FROSCH
ZIEL	RICHTUNG	GRAS	VIEH
KLIPPE	ABGRUND	TRAUM	WIRKLICHKEIT
SALAT	GARTEN	DÄMMERUNG	MORGENGRAUEN
DICKICHT	WALD	SEEGANG	DAMPFER
GÖTTIN	GEBET	BUNGALOW	SIEDLUNG
ANFÜHRER	CHEF	GEISEL	GEFANGENER
MUSIKER	AKKORDEON	POSTKUTSCHE	PFERD
GLÜCK	ZUFALL	DISZIPLIN	GEHORSAM
HIMMEL	FIRMAMENT	SCHMETTERLING	BLÜTE
ERGÄNZUNG	ZUSATZ	GNADE	BARMHERZIGKEIT
ZIMMER	ECKE	ANSTAND	SITTE
POLIZIST	WACHE	BERG	HÜTTE
SCHÜLER	DOZENT	MACHT	HERRSCHER
SCHLEMMER	LECKERBISSEN	FREUND	VERTRAUEN
MÖNCH	NONNE	BLICK	PERSPEKTIVE
MOOR	SUMPF	VERSCHLEIERUNG	KOPFTUCH
SAUERSTOFF	LUFT	EHE	VERLOBUNG

Supplemental Table S2. Sleep parameters for the first three experiments including highly suggestible subjects

	Experiment 1		Experiment 2		Experiment 3	
in % of TST	Hypnosis	Control	Hypnosis	Control	Incomprehen-sible	Control
N1	10.50 ± 1.52	9.38 ± 1.11	15.03 ± 2.43	12.78 ± 1.92	4.73 ± 0.90	12.58 ± 7.11
N2	40.99 ± 3.47	43.07 ± 4.99	49.29 ± 5.32	44.92 ± 4.14	44.80 ± 6.08	50.44 ± 6.38
SWS	**30.60 ± 4.89** [b]	**16.89 ± 4.38**	22.33 ± 3.91	24.16 ± 3.20	25.72 ± 5.50	26.64 ± 6.83
REM	10.56 ± 2.99	8.32 ± 2.96	4.36 ± 2.05	5.39 ± 1.79	4.54 ± 2.50	2.89 ± 1.40
WASO	**7.34 ± 3.88** [a]	**22.34 ± 7.60**	9.20 ± 3.87	12.72 ± 4.45	12.50 ± 5.54	14.12 ± 7.82
In min						
Time in bed	92.32 ± 1.26	92.13 ± 1.00	90.18 ± 0.40	90.46 ± 0.67	89.86 ± .30	90.36 ± 0.81
TST	74.11 ± 4.89	75.68 ± 4.86	64.39 ± 6.24	67.29 ± 5.60	70.42 ± 7.48	70.58 ± 8.72
WASO	**5.00 ± 2.39** [b]	**15.75 ± 5.06**	6.00 ± 2.63	7.32 ± 2.68	7.25 ± 2.62	5.29 ± 3.16
Sleep latency	15.18 ± 4.06	15.29 ± 3.70	14.93 ± 2.60	20.18 ± 4.12	9.54 ± 2.20	19.92 ± 8.56
SWS latency	**12.82 ± .90** [b]	**27.89 ± 6.81**	19.61 ±4.18	15.93 ± 2.10	27.42 ± 7.84	19.08 ± 6.47
REM sleep latency	56.61 ± 4.29	63.39 ± 4.86	65.04 ± 5.12	64.43 ± 3.80	67.04 ± 7.42	62.08 ± 8.49
Theta during listening	**13.46 ± 2.16** [b]	**11.05 ± 1.82**	14.69 ± 1.37	16.48 ± 2.05		
SWA parietal	**77.30 ± 2.45** [b]	**70.64 ± 2.68**	70.16 ± 2.29	72.24 ± 2.57		
NREM cycles total	1.86 ± .14	1.93 ± .27	1.43 ± .23	1.50 ± .17		

Notes. Values are means ± standard error of the mean. Stage 1 and 2 sleep (N1 and N2), slow-wave sleep (SWS), rapid eye movement sleep (REM), time awake after sleep onset (WASO), total sleep time (TST), slow-wave sleep latency (SWS latency), theta overall mean, and slow-wave activity (SWA) in parietal derivations, nonrapid eye movement (NREM). Significant differences are indicated by [a]$P \geq 0.07$; [b]$P < 0.05$.

Supplemental Table S3. Sleep parameters for the last two experiments including low suggestible subjects.

	Experiment 4		Experiment 5	
in % of TST	Hypnosis	Control	Hypnosis	Control
N1	8.99 ± 1.35	8.19 ± 1.22	7.60 ± 2.40	4.55 ± 0.59
N2	45.71 ± 6.06	39.20 ± 4.60	45.99 ± 6.55	50.52 ± 3.97
SWS	**18.47 ± 3.87** [b]	**28.12 ± 4.67**	27.16 ± 4.76	34.70 ± 14.59
REM	11.77 ± 3.90	11.38 ± 3.24	**0.60 ± 0.60** [b]	**8.22 ± 2.62**
WASO	8.63 ± 4.41	5.82 ± 1.50	17.35 ± 8.27	1.97 ± 0.42
In min				
Time in bed	91.6 ± 0.94	95.79 ± 2.18	90.00 ± 0.18	89.77 ± 0.41
TST	**70.00 ± 5.89** [b]	**79.53 ± 6.22**	70.63 ± 6.61	78.50 ± 3.26
WASO	5.93 ± 2.84	4.70 ± 1.19	**12.29 ± 5.69** [a]	**1.50 ± 0.31**
Sleep latency	14.70 ± 6.07	16.37 ± 6.34	9.88 ± 2.31	7.63 ± 1.85
SWS latency	24.60 ± 6.80	18.03 ± 5.14	28.50 ± 6.86	19.25 ± 3.49
REM sleep latency	49.00 ± 8.12	63.70 ± 5.54	77.79 ± 2.95	70.58 ± 3.92
Theta during listening	14.38 ± 1.23	15.09 ± 1.57		
SWA parietal	73.61 ± 2.30	75.59 ± 2.45		
NREM cycles total	1.73 ± 0.21	1.87 ± 0.19		

Notes. Values are means ± standard error of the mean. Stage 1 and 2 sleep (N1 and N2), slow-wave sleep (SWS), rapid eye movement (REM) sleep, time awake after sleep onset (WASO), total sleep time (TST), slow-wave sleep latency (SWS latency), nonrapid eye movement (NREM). Significant differences are indicated by [a]$P \geq 0.08$; [b]$P < 0.05$.

Supplemental Table S4. Overview of how many subjects reported to have listened or not focused on the text or tried to ignore the voice

	Text	Listened, tried to imagine	Not focusing on the voice	Ignore the voice	Others
Exp. 1 (n = 14)	Hypnosis	9 (64.3%)	5 (35.7%)	0	0
	Control	3 (21.4%)	8 (57.1%)	3 (21.4%)	0
Exp.2 (n = 13)	Hypnosis	9 (69.2%)	3 (23.1%)	0	1 (7.7%)
	Control	3 (23.1%)	8 (61.5%)	2 (15.4%)	0
Exp. 3 (n = 12)	Incompr.	0	4 (33.3%)	7 (58.3%)	1 (8.3%)
	Control	3 (25%)	7 (58.3%)	2 (16.7%)	0
Exp. 4 (n = 15)	Hypnosis	8 (53.3%)	6 (40%)	0	1 (6.7%)
	Control	2 (13.3%)	6 (40%)	4 (26.7%)	3 (20%)
Exp. 5 (n = 12)	Hypnosis	8 (66.7%)	1 (8.3%)	2 (16.7%)	1 (8.3%)
	Control	6 (50%)	5 (41.7%)	1 (8.3%)	0

Notes. Values represent total number of subjects (percentage in brackets). experiment (Exp).

Supplemental Table S5. Performance on memory tasks

Word pair learning		**Hypnosis**	**Control**	*t*	P
Exp. 1	Encoding	40.36 ± 2.55	37.57 ± 3.35	*t*(13) = 1.29	0.22
	Recall	41.43 ± 2.71	37.71 ± 3.40	*t*(13) = 1.39	0.19
	% Change	102.92 ± 3.34	100.41 ± 1.30	*t*(13) = 0.73	0.48
Exp. 2	Encoding	40.00 ± 3.40	38.00 ± 3.05	*t*(13) = 0.78	0.45
	Recall	38.36 ±3.59	38.14 ± 3.46	*t*(13) = 0.08	0.94
	% Change	94.96 ± 4.78	98.82 ± 2.63	*t*(13) = -0.99	0.34
Exp. 3	Encoding	34.92 ± 2.98	31.00 ± 2.53	*t*(11) = 0.99	0.35
	Recall	35.33 ± 3.37	31.58 ± 2.76	*t*(11) = 0.92	0.38
	% Change	100.23 ± 2.53	101.79 ± 2.90	*t*(11) = -0.40	0.70
Exp. 4	Encoding	37.07 ± 3.40	31.20 ± 3.64	*t*(14) = 2.62	0.02
	Recall	37.13 ± 3.46	31.27 ± 3.56	*t*(14) = 2.27	0.04
	% Change	106.58 ± 8.76	101.33 ± 3.92	*t*(14) = 0.53	0.60
Exp. 5	Encoding	32.92 ± 4.45	32.92 ± 4.04	*t*(11) = 0.01	0.99
	Recall	33.17 ± 4.28	33.75 ± 4.28	*t*(11) = -0.13	0.90
	% Change	99.74 ± 4.40	99.59 ± 4.91	*t*(11) = 0.02	0.98
Sequence finger tapping		**Hypnosis**	**Control**	*t*	P
Exp. 1	Encoding	17.38 ± 0.89	16.83 ±1.00	*t*(13) = 0.78	0.45
	Recall	20.22 ± 0.78	18.95 ± 1.00	*t*(13) = 1.53	0.15

	% Change	118.82 ± 6.14	114.23 ± 4.14	$t(13) = 0.78$	0.45
	Encoding	18.22 ±1.11	17.64 ± 1.07	$t(13) = 0.48$	0.64
Exp. 2	Recall	20.98 ± 1.53	20.14 ± 1.56	$t(13) = 0.96$	0.35
	% Change	116.62 ± 6.58	113.54 ± 5.44	$t(13) = 0.48$	0.64
	Encoding	15.58 ± 0.83	16.31 ± 0.74	$t(11) = -1.07$	0.31
Exp. 3	Recall	18.42 ± 1.43	19.28 ± 1.25	$t(11) = -0.70$	0.50
	% Change	117.37 ± 5.36	117.80 ± 4.66	$t(11) = -0.07$	0.95
	Encoding	15.86 ± 1.16	15.69 ± 0.92	$t(13) = -0.45$	0.66
Exp. 4	Recall	18.90 ± 1.27	19.48 ± 1.45	$t(13) = -0.65$	0.53
	% Change	126.48 ± 5.21	132.18 ± 12.79	$t(13) = -0.45$	0.66
	Encoding	16.11 ± 1.13	14.92 ± 1.66	$t(11) = 0.88$	0.40
Exp. 5	Recall	19.58 ± 1.41	19.20 ± 1.77	$t(11) = 0.24$	0.82
	% Change	119.79 ± 5.19	124.81 ± 5.45	$t(11) = -0.56$	0.59

Notes. Values are absolute values of encoding level and percentage of change (amount of recall with performance at encoding set to 100% ± standard error of the mean). Right column indicates P values from pairwise *t*-tests for encoding, recall, and change. Experiment (Exp).

Supplemental Table S6. Overview how many subjects reached rapid eye movement sleep separately for condition, including the results of the McNemar test for paired proportions

	Exp. 1		Exp. 2		Exp. 4	
	Hypnosis	**Control**	**Hypnosis**	**Control**	**Hypnosis**	**Control**
Subjects reaching REM sleep	10	7	5	6	10	8
Subjects not reaching REM sleep	4	7	9	8	5	7
p	.25		.99		.73	

Notes. Exp, experiment; REM, rapid eye movement.

Supplemental Table S7. Number of nonrapid eye movement cycles until the first occurrence of rapid eye movement sleep and total amount of nonrapid eye movement cycles in the 90 min nap (± standard error of the mean).

		Hypnosis	**Control**	*t*	P
NREM cycles until first REM	Exp. 1	1.5 ± 0.14	1.71 ± 0.22	-1.15	0.27
	Exp. 2	1.36 ± 0.20	1.29 ± 0.16	0.37	0.72
	Exp.4	1.40 ± 0.19	1.67 ± 0.21	-1.7	0.10
NREM cycles Before wake	Exp. 1	1.29 ± 0.16	1.57 ± 0.25	-1.47	0.17
	Exp. 2	1.07 ± 0.25	1.07 ± 0.20	< 0.001	> 0.99
	Exp. 4	1.20 ± 0.18	1.33 ± 0.21	-0.70	0.50
NREM cycles total	Exp. 1	1.86 ± 0.14	1.93 ± 0.27	-0.37	0.72
	Exp. 2	1.43 ± 0.23	1.50 ± 0.17	-0.32	0.75
	Exp. 4	1.73 ± 0.21	1.87 ± 0.19	-0.62	0.55

Notes. Exp, experiment; NREM, nonrapid eye movement; REM, rapid eye movement.

Supplemental Table S8. Data of fast spindle density in Pz, slow spindle density in Fz and electroencephalographic sigma power (averaged across all electrodes) during nonrapid eye movement

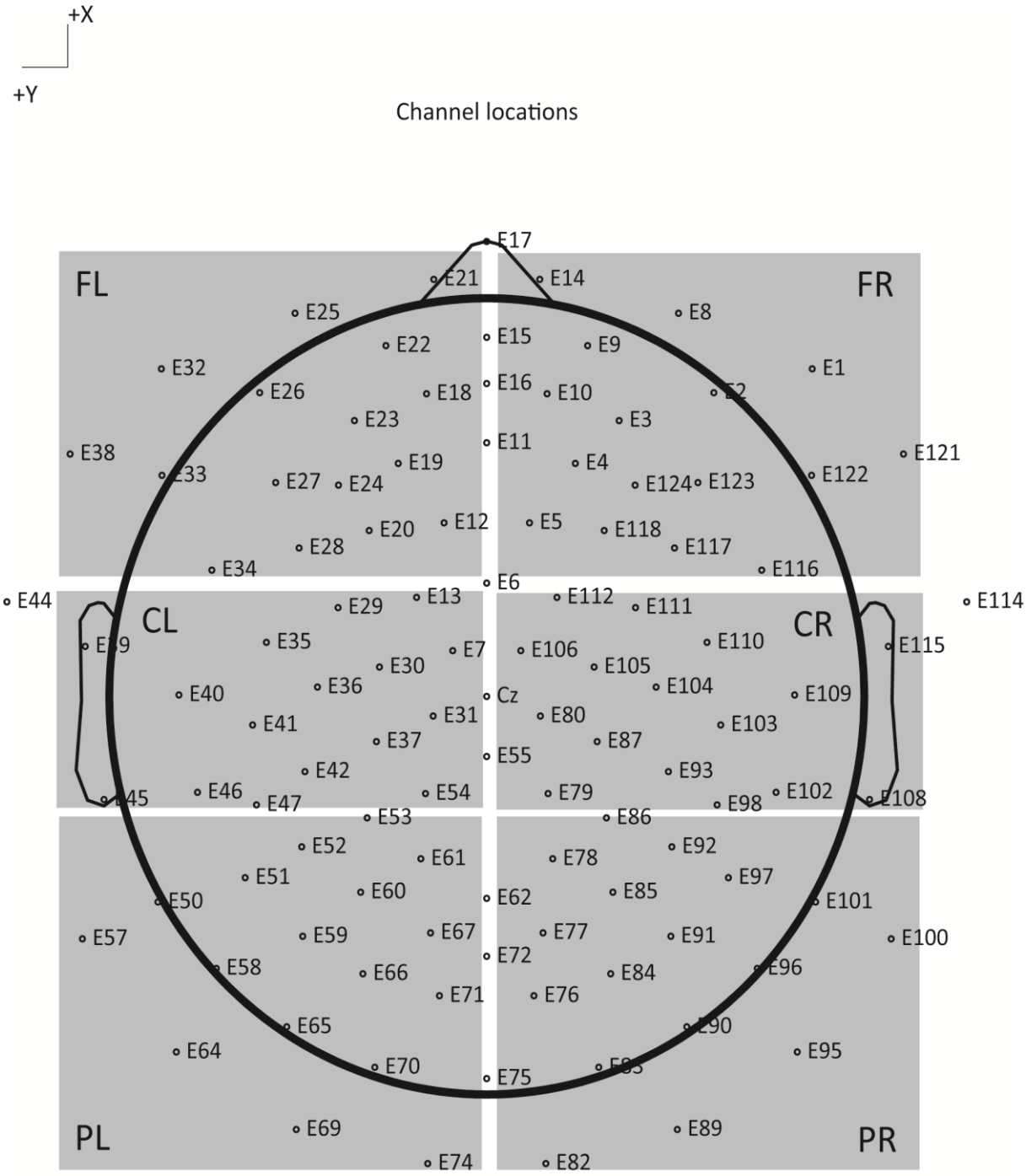
		Hypnosis	**Control**	*t*	P
Fast spindle density at electrode Pz	Exp. 1	2.31 ± 0.31	2.03 ± 0.32	*t*(13) = 1.55	0.15
	Exp. 2	1.65 ± 0.30	1.95 ± 0.30	*t*(13) = -1.94	0.08
	Exp. 4	1.86 ± 0.30	1.89 ± 0.31	*t*(14) = -0.24	0.82
Slow spindle density at electrode Fz	Exp. 1	2.90 ± 0.34	2.53 ± 0.31	*t*(13) = 2.00	0.07
	Exp. 2	2.16 ± 0.42	2.42 ± 0.45	*t*(13) = -0.85	0.41
	Exp. 4	1.94 ± 0.26	2.04 ± 0.28	*t*(14) = -0.67	0.51
Mean sigma power (11 – 15 Hz)	Exp. 1	4.39 ± 0.85	5.02 ± 0.68	*t*(12) = -1.20	0.25
	Exp. 2	4.21 ± 0.34	4.58 ± 0.71	*t*(13) = -0.62	0.55
	Exp. 4	4.12 ± 0.55	3.90 ± 0.51	*t*(14) = 0.43	0.68

Supplemental Table S9. Correlations between hypnosis-induced increases in minutes spent in slow-wave sleep and changes in slow-wave activity during nonrapid eye movement sleep and changes in theta activity during listening in experiment 1

	SWS [min]	L frontal SWA	R frontal SWA	L central SWA	R central SWA	L parietal SWA	R parietal SWA
SWS [min]		0.81 0.*001* [b]	0.86 *0.001* [b]	0.85 *0.001* [b]	0.89 *0.001* [b]	0.91 *0.001* [b]	0.89 *0.001* [b]
L parietal theta	0.59 *0.025* [a]	0.53 *0.05* [a]	0.54 *0.05* [a]	0.47 *0.09*	0.52 *0.06*	0.54 *0.05* [a]	0.51 *0.06*
R parietal theta	*0.59* *0.026* [a]	0.51 *0.07*	0.51 *0.06*	0.44 *0.12*	0.49 *0.07*	0.51 *0.06*	0.47 *0.09*

Notes. Correlations were analyzed with the differences in parameters between hypnosis and control condition. For a definition of frontal, central and parietal regions see supporting methods. L, left; R, right; SWA, slow-wave activity; SWS, slow-wave sleep. [a]$P < 0.05$; [b]$P < 0.001$.

Supplemental Figure S1. Topographical regions used for the statistical analysis of the EEG data. We defined six topographical regions (as indicated by gray areas): frontal left (FL), frontal right (FR), central left (CL), central right (CR), parietal left (PL), parietal right (PR).



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4.3. Improving Sleep and Cognition by Hypnotic Suggestion in the Elderly[3]

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The authors declare that they have no conflict of interest.

[3] A similar version of this manuscript has been submitted for publication in „PNAS“

Abstract

Sleep quality markedly declines across the human lifespan. Particularly the amount of slow-wave sleep (SWS) decreases with age and this decrease is paralleled by a loss of cognitive functioning in the elderly. Here we show in healthy elderly females that the amount of SWS can be extended by a hypnotic suggestion "to sleep deeper" before sleep. In a placebo-controlled cross-over design, participants listened to hypnotic suggestions or a control tape before a midday nap while high density electroencephalography was recorded. After the hypnotic suggestion, we observed a 57% increase in SWS in females suggestible to hypnosis as compared to the control condition. Furthermore, left frontal slow-wave activity (SWA), characteristic for SWS, was significantly increased, followed by a significant improvement in prefrontal cognitive functioning after sleep. Our results suggest that hypnotic suggestions might be a successful alternative for widely-used sleep-enhancing medication to extend SWS and improve cognition in the elderly.

Keywords: Hypnosis, Slow-Wave Sleep, Aging, Cognitive function, High density EEG,

Introduction

Sleep is vital for our health and well-being, and particularly slow-wave sleep (SWS) has been proven critical for restoration and optimal cognitive brain functioning (Anderson & Horne, 2003; Finelli, Borbély, & Achermann, 2001; Van Der Werf et al., 2009). In the elderly, sleep quality is typically strongly reduced and accompanied by an increased rate of clinically relevant sleep disturbances as well as extensive use of sleep-inducing medication (Crowley, 2011; Foley et al., 1995; SFA, 2009). In particular, SWS continuously decreases across the human life span, possibly reflecting the loss of synaptic density and neural functioning (Mander et al., 2013). SWS is strongly reduced in aging related disorders like mild cognitive dementia and associated with cortical thinning and prefrontal cortical atrophy (Mander et al., 2013; Sanchez-Espinosa, Atienza, & Cantero, 2014). Furthermore, reduced sleep quality and sleep fragmentation in non-demented elderly participants are reliable predictors for later cognitive decline, increased amyloid beta disposition and development of Alzheimer's disease after several years (Keage et al., 2012; Lim, Kowgier, Yu, Buchman, & Bennett, 2013; see Pace-schott & Spencer, 2014 for a review; Spira et al., 2013). Frequently prescribed sleep-inducing drugs typically hinder the occurrence of SWS, loose their efficacy during long-term treatment, have adverse side effects and often a high risk of addiction (Hajak & Rüther, 2006; Riemann & Perlis, 2009). Therefore, the development of efficient and risk-free approaches to improve sleep and particularly SWS in the elderly is highly needed.

While the sleep-disturbing effects of negative thoughts, stress, and rumination are widely accepted (Saper, Cano, & Scammell, 2005; Van Reeth et al., 2000), research on the possibility of positively influencing sleep by psychological interventions is rather scarce. A reason might be the observation that cognitively "wanting" to improve sleep quality typically fails or can even be counterproductive (Ansfield, Wegner, & Bowser, 1996). Thus, subconscious influences might prove more effective in this regard, which could be exerted under the state of hypnosis. Hypnosis can be defined as a state of changed mental activity after an induction procedure which mainly encompasses a state of focused attention and absorption (Oakley & Halligan, 2009). Importantly, during the state of hypnosis, suggestible subjects respond more easily to hypnotic suggestions. These are statements given during induction or afterwards, intended to change or influence behavior. They can include e.g., decrease of pain, motor paralysis or posthypnotic amnesia, and recent cognitive neuroscience research has successfully demonstrated effects of these suggestions on underlying brain activation using objective neuroimaging methods (Bell, Oakley, Halligan, & Deeley, 2011; Cojan et al., 2009; Cojan, Archimi, Cheseaux, Waber, & Vuilleumier, 2013; Kihlstrom, 2013; Mendelsohn, Chalamish, Solomonovich, & Dudai, 2008; Posner & Rothbart, 2011). In therapeutical contexts, hypnosis has been proven an effective tool in reducing pain, anxiety and stress related disorders

(Bongartz, Flammer, & Schwonke, 2002; Flammer & Bongartz, 2003), and several studies provide evidence for a beneficial effect of hypnosis on sleep disturbances and insomnias (Borkovec & Fowles, 1972; Schlarb, 2005; Stanton, 1989). Very recently, we have shown that listening to a hypnotic suggestion before sleep strongly extends the amount of SWS and slow-wave activity (SWA, 0.5–4.5 Hz) in young healthy females suggestible to hypnosis (Cordi, Schlarb, & Rasch, 2014). SWA is regarded as the hallmark oscillatory brain activity characterizing SWS and has been functionally related to processes of brain plasticity and synaptic density (Huber, Ghilardi, Massimini, & Tononi, 2004). Control experiments confirmed that the type of hypnotic suggestions was critical for the beneficial effect on SWS and excluded alternative explanation like general relaxation and demand characteristics. Interestingly, less suggestible females did not benefit from the hypnotic suggestions, even when asked to simulate the effects of a hypnotized person (see Cordi et al., 2014). However, it remains an open question whether these results are robust and generalizable to elderly participants. In addition, it remains elusive whether hypnosis-induced increases in SWS and frontal SWA result in an improvement in cognitive functions. We predicted that SWS and SWA will also increase after hypnotic suggestions in highly suggestible elderly females. Further, particularly in the elderly, prefrontal SWA has been recently associated with age-related prefrontal brain atrophy and cognitive functions (Mander et al., 2013). Thus, we expected performance in tasks recruiting frontal areas to improve after SWA increases.

Results

Influence of the hypnotic suggestion on subsequent SWS

Thirty-nine healthy elderly females (mean age 67.08 ± 4.39 years ± standard deviation [*SD*])) were included in the analysis. Prior to the experiment, all participants were classified as highly (n = 19) vs. low suggestible (n = 20) according to the Harvard Group Scale of Hypnotic Susceptibility (HGSHS) (Bongartz, 1985). After an adaptation nap in the sleep laboratory, all participants came for two experimental midday naps of 90 min to the sleep laboratory. The elderly females listened either to the hypnosis or the control tape in a counterbalanced order for 13 min while lying in bed (see Figure 1A and B, for a summary of the procedure). The hypnosis tape consisted of a standard hypnosis induction procedure, followed by hypnotic suggestions to sleep deeper (i.e., a fish swimming deeper and deeper in the sea, see methods). The control text was a neutral text on mineral deposits. Memory functions were tested before and after the nap and sleep was recorded using high density EEG and standard polysomnography.

As predicted, listening to hypnotic suggestions "to sleep deeper" before sleep strongly extended the amount of time spent in deep sleep in elderly females suggestible to hypnosis. Importantly, the hypnotic suggestion before sleep increased the amount of SWS to 157.69 ± 19.66%, with the amount of SWS after the control text set to 100% (see Figure 1C and Table 1). In contrast, females not suggestible to hypnosis did not benefit from the intervention (repeated measures ANOVA with the factors suggestibility (high vs. low) and condition (hypnosis vs. control text), $F(1, 37) = 5.88$, $p = .020$, $\eta^2 = 0.14$). Planned pairwise comparisons confirmed that after listening to the hypnotic tape, highly suggestible females spent on average 27.48 ± 3.43% (20.58 ± 3.01 min) of their time in bed in SWS as compared to only 17.43 ± 4.03% SWS (11.84 ± 2.92 min) after listening to the control tape ($t(18) = 2.27$, $p = .036$, $t(18) = 2.86$, $p = .01$ for SWS % and min, respectively). In addition, highly suggestible females reached SWS significantly earlier after hypnotic suggestions (15.05 ± 3.61 min) than after the control text (27.66 ± 5.88 min; $F(1, 37) = 4.34$, $p = .04$, $\eta^2 = 0.11$; $t(18) = 2.23$, $p = .04$, see Table 1 and S1). In low suggestible participants, the amount of SWS and SWS latency did not differ between conditions (both $p > .30$). SWS latency in both conditions did also not differ from the adaptation night (both conditions $p > .60$). Furthermore, we observed no effects of hypnotic suggestions on any other sleep stage (all $p > .40$, Table S1). Average sleep latencies did also not differ between hypnosis and control conditions, neither for highly suggestible (21.71 ± 4.60 vs. 18.97 ± 4.44 min, $t(18) = .65$, $p = .52$) nor for low suggestible participants (16.75 ± 2.33 vs. 12.70 ± 2.94 min, $t(19) = 1.77$, $p = .09$). Please note that sleep latencies were on average longer (see also Table S1) than the duration of the audio tapes (13 min), excluding that our reported results might be explained by falling asleep during the listening period.

Figure 1. Overview of the Session and Main Findings

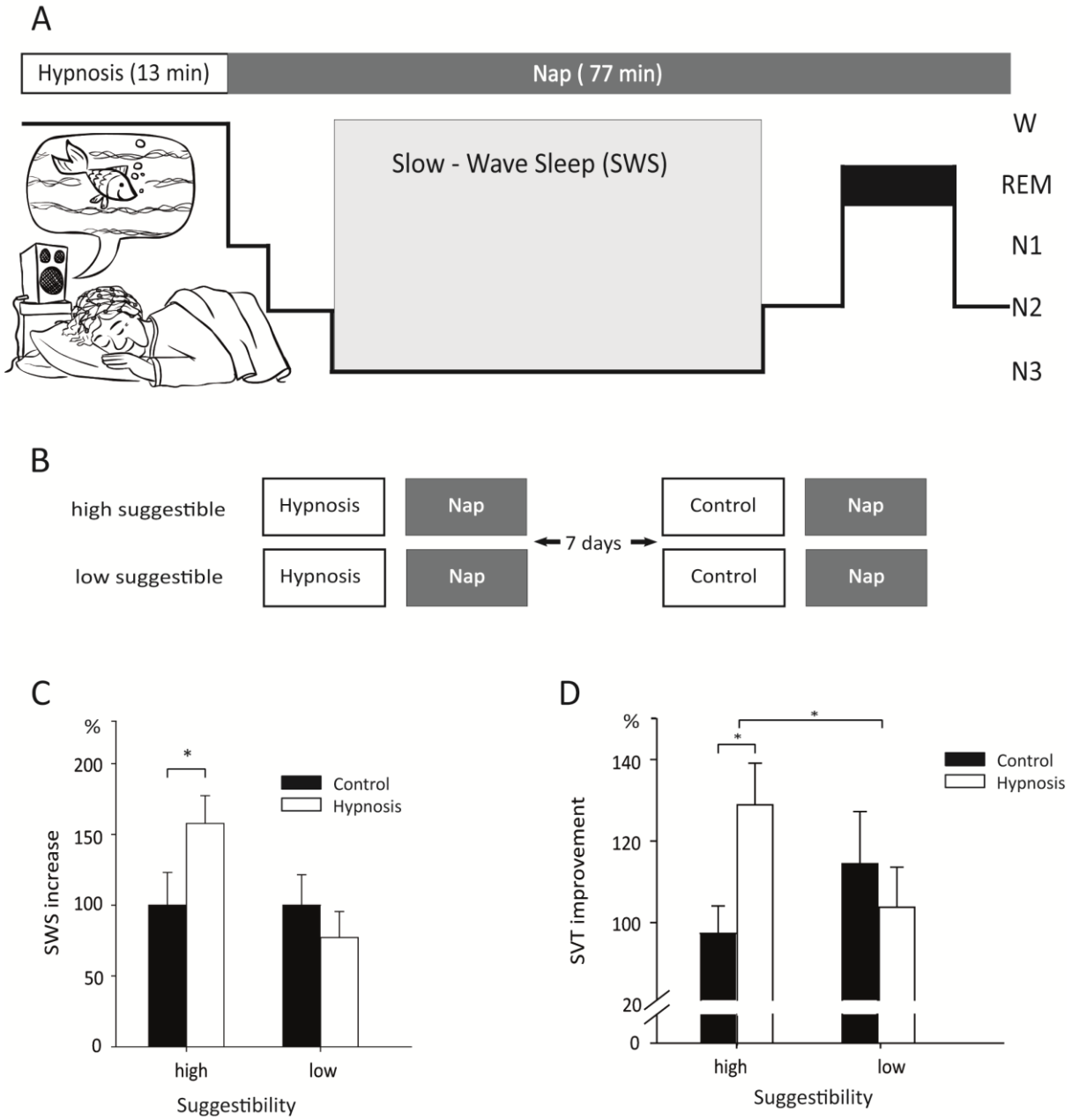

Figure 1. Figure 1 gives an overview of the session procedure and the main findings. (A) Subjects listened to the hypnotic suggestions (a fish swimming in the sea) or a control text in a randomized order while lying in bed. Immediately afterwards they were allowed to fall asleep and were awakened after a total of 90 minutes. (B) Both sessions of the within-subjects design were spaced one week apart. (C) Displays means of relative SWS increases after hypnotic suggestions with SWS amounts in the control naps set to 100% to nap after hypnotic suggestions and SEM of high and low suggestible younger and older adults. The pattern of increased SWS after hypnotic suggestions as demonstrated in younger adults could be replicated for older adults. (D) Displays the increase in prefrontal memory performance from presleep to postsleep for both groups and conditions (hypnosis versus control condition). *: $p < .05$, **: $p < .01$.

Influence of the hypnotic suggestion on slow-wave activity during sleep

In accordance with the benefits on SWS, we observed a significant increase in prefrontal SWA power after hypnotic suggestions, which was particularly pronounced in left prefrontal brain areas (ANOVA with the factors suggestibility (high vs. low), condition (hypnosis vs. control) and hemisphere (left vs. right) $F(1, 37) = 6.74$, $p = .013$, $\eta^2 = .15$; substantiated by a statistical trend in the two-way interaction suggestibility * condition ($F(1, 37) = 2.90$, $p = .097$, $\eta^2 = .07$). Planned pairwise comparisons confirmed that left prefrontal SWA power in suggestible participants was increased in the hypnosis as compared to the control condition (104.99 ± 2.62%, with the control condition set to 100%, ($t(18) = 2.17$, $p = .044$, see Figure 2B and Table 1).

Table 1. SWS Amount in Older Adults and Young Adults

	Older adults		Younger adults	
	Hypnosis	**Control**	**Hypnosis**	**Control**
% SWS (with control condition set to 100%)				
HS	157.7 ± 19.7%	100.0 ± 23.1%*	181.2 ± 29.0%	100.0 ± 25.9%*
LS	77.1 ± 18.4%	100.0 ± 21.5%	65.7 ± 13.8%	100.0 ± 16.6%*
% SWS (of total time in bed)				
HS	27.5 ± 3.4%	17.4 ± 4.0%*	30.6 ± 4.9%	16.9 ± 4.4%*
LS	18.8 ± 4.5%	24.4 ± 5.2%	18.5 ± 3.9%	28.1 ± 4.7%*
Minutes spent in SWS				
HS	20.6 ± 3.0 min	11.8 ± 2.9 min*	23.4 ± 4.3 min	14.1 ± 3.6 min*
LS	12.3 ± 3.2 min	18.9 ± 4.4 min	14.6 ± 3.3 min	24.3 ± 4.2 min*
SWS latency				
HS	15.1 ± 3.6 min	27.7 ± 5.9 min*	12.8 ± 0.9 min	27.9 ± 6.8 min*
LS	25.6 ± 5.3 min	21.6 ± 5.4 min	24.6 ± 6.8 min	18.0 ± 5.1 min
SWA Power (left frontal) in % Ptot, with control condition set to 100%				
HS	105.0 ± 2.6%	100.0 ± 2.5%*	105.3 ± 9.4%	100.0 ± 9.0%*
LS	98.1 ± 2.7%	100.0 ± 2.1%	99.5 ± 6.7%	100.0 ± 9.4%

Notes. Values are means ± SEM. %SWS: %SWS in the control condition set to 100%. HS = highly suggestible, LS = low suggestible. Relative SWA: relative SWA Power with total power set to 100%. SWA Power: relative SWA Power with control condition set to 100% (adjusted values for older adults). Average time in bed was 89.5 ± .15 min in older adults and 92.9 + .63 min in younger adults and did not differ between conditions (both $p > .09$). *:$p \leq .05$ in planned pairwise comparisons.

Influence of the hypnotic suggestion on prefrontal cognitive functioning

In a last step, we tested whether the robust hypnosis-induced increases in SWS and prefrontal SWA are reflected in cognitive benefits in tasks recruiting prefrontal areas in the elderly

participants. Importantly, the semantic verbal fluency task (SVT) is sensitive for prefrontal cortex functions and for healthy aging (Haugrud, Lanting, & Crossley, 2010; Miceli, Caltagirone, Gainotti, Masullo, & Silveri, 1981; Ramier & Hécaen, 1970). Suggestible participants exhibited a significant improvement in this task after hypnosis-induced increases in SWS, whereas no effects were observed for low suggestible females (interaction suggestibility * condition; $F(1,37) = 4.24$, $p = .047$, $\eta^2 = .10$). Planned pairwise comparisons confirmed that suggestible elderly females exhibited increased performance in the SVT task (128.87 ± 10.22%, with pre-sleep performance set to 100%) as compared to pre-sleep performance ($t(18) = 2.83$, $p = .01$) as well as compared to the performance change across the control nap (97.33 ± 6.74%), $t(18) = 2.69$, $p = .015$, see Figure 1D and Table S2). These changes were not observed in low suggestible participants (all $p > .50$). Similarly, hippocampus-dependent declarative memory consolidation of word pairs known to depend on early, SWS rich sleep (Plihal & Born, 1997) descriptively reflected the pattern of hypnosis-induced SWS changes. However, effects in consolidation reached only a statistical trend ($F(1, 34) = 3.24$, $p = .08$, $\eta^2 = .09$, see supplementary Table S3). Generally, our results on cognitive measures were not confounded by differences in vigilance as we observed no significant influences of SWS / SWA changes in the psychomotor vigilance test (PVT) tested directly after the nap ($p > .80$ for highly and low suggestible subjects). Overall, the subjective sleep quality ratings were significantly associated with percentage of SWS and frontal left SWA power in both groups and both conditions, suggesting that increased SWS and SWA generally contribute to subjective feelings of better sleep quality (%SWS: $r(36) = .42$, $p = .008$ and $r(35) = .31$, $p = .06$; frontal left SWA: $r(37) = .55$, $p < .001$ and $r(36) = .38$, $p = .02$; for hypnosis and control condition, respectively, see Figure 2C and 2D).

Figure 2. Overview of the Effects of Hypnotic Suggestions on SWA

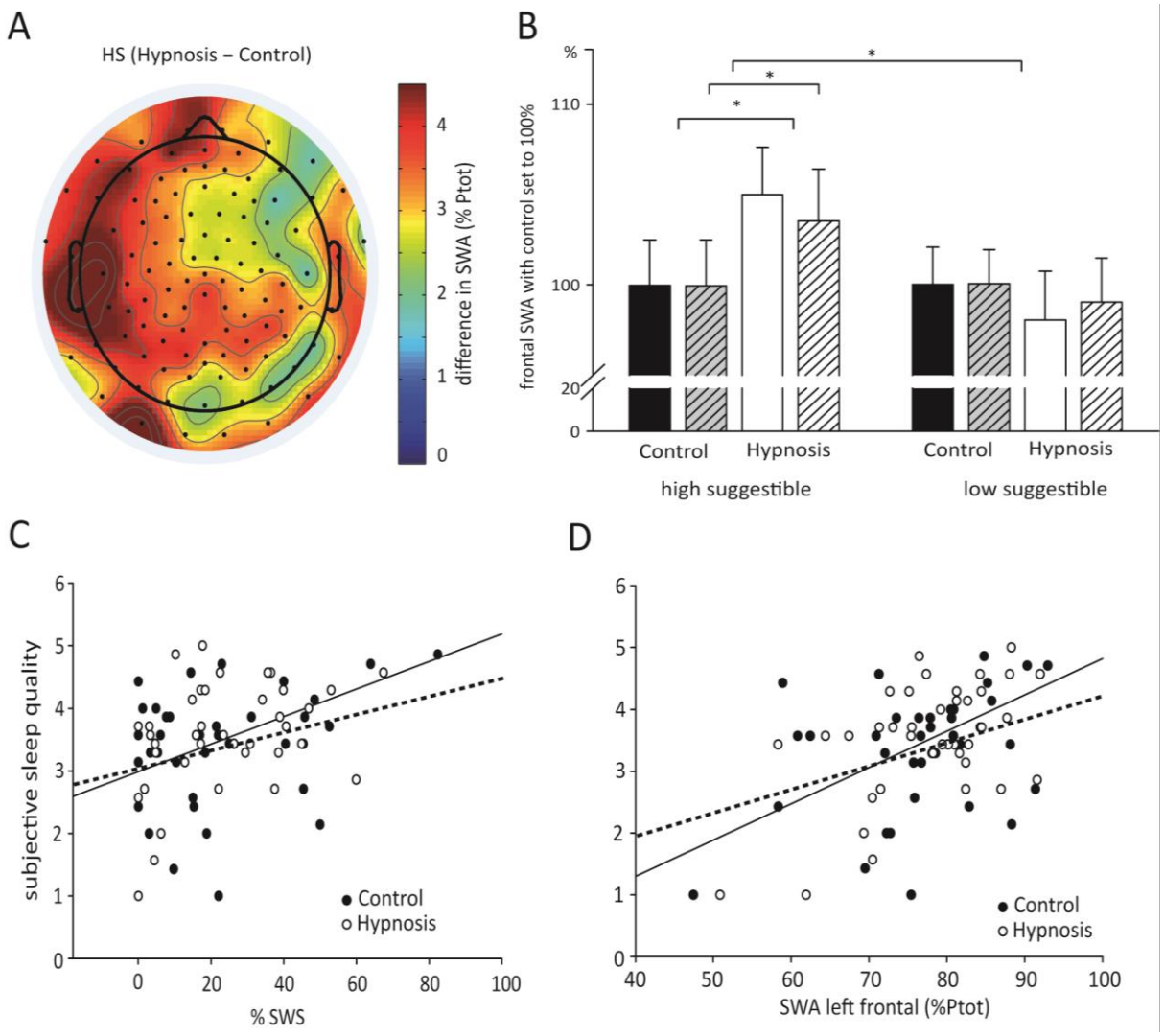

Figure 2. Figure 2 summarizes the data on SWA and correlations between objective and subjective sleep measures. (A) Displays differences in relative NREM SWA (Ptot = with total power set to 100%) in highly suggestible subjects (HS) after hypnosis versus control condition. (B) demonstrates the threefold interaction between suggestibility, text and hemisphere found for SWA, which resulted from SWA difference in highly suggestibles between sleep after hypnotic suggestions and after control text, significantly differing in the left hemisphere (for region definition see Figure S1). (C) Subjective ratings of sleep quality were correlated with % SWS separately for conditions (black dots represent data from control condition, white dots from hypnosis) and (D) SWA in left frontal derivations. Dotted lines are regression lines of the hypnosis condition. Error bars represent standard errors of the mean. *: $p < .05$

Comparison between younger and older adults

Using a basically identical experimental design as reported here, we have previously published the finding that listening to hypnotic suggestions before sleep extends SWS and increases SWA in younger female participants (aged 23.27 ± 3.17 years, see Cordi et al., 2014). In this prior work we have already experimentally confirmed that the beneficial effect of hypnotic suggestions on SWS critically depends on the type of the hypnotic suggestion and successfully excluded alternative explanations, i.e., generally relaxing effect of the hypnosis tape or demand characteristics. Therefore we directly compared our current findings in elderly females with respect to hypnosis-induced increases in SWS to young adults. The result pattern was basically identical and robust, revealing strong hypnosis-induced increases in SWS in both suggestible young (181.2 ± 28.95%) as well as elderly females (157.69 ± 19.66%, with SWS amount after the control text set to 100%). No or even opposite effects were observed for low suggestible participants (see Table 1). Combining relative SWS amounts (with %SWS in the control condition set to 100%) from both data sets revealed a highly significant interaction between suggestibility (high vs. low) and condition (hypnosis vs. control) $F(1,64) = 18.10$, $p < .001$, $\eta^2 = .22$, indicating the robustness of the benefits of hypnotic suggestions on SWS. Comparable effects were observed for percentage of SWS, minutes spent in SWS and SWS latency (all $p < 0.002$, see Table 1). Similarly, prefrontal SWA was strongly influenced by the experimental condition and suggestibility ($F(1,63) = 5.23$, $p = .026$, $\eta^2 = .08$, see Table 1). Importantly, listening to hypnotic suggestions before sleep extended the amount of sleep and increased SWA independently of age, as indicated by a complete lack of interaction effects with age (all $p > .60$).

Discussion

In confirmation of our hypothesis, listening to a hypnotic suggestion “to sleep deeper” significantly extended the amount of SWS during a midday nap in healthy elderly females. In addition, left prefrontal SWA was significantly increased during sleep after listening to the hypnosis and performance in a prefrontal-dependent verbal fluency task was significantly improved. The benefits of hypnosis on sleep in elderly suggestible females were highly comparable to the effects of hypnotic suggestion on sleep in younger suggestible females as reported previously (Cordi et al., 2014). Thus, the usage of hypnotic suggestion to extend SWS in suggestible females appears to be robust, replicable and largely age-independent.

It might be argued that the beneficial effects of hypnotic suggestions on SWS are unspecific and rather due to the relaxing nature of the hypnotic text or the expectations of the participants of being hypnotized. We can safely exclude these interpretations due to several control experiments in young females (see Cordi et al., 2014): Young suggestible females expecting that the hypnosis will

extend their SWS listened to same hypnotic vs. control text as used in the current experiment. However, the hypnotic suggestion in this group was altered now suggesting “to sleep shallower” (i.e., a boat resting on the surface). Here, we observed no significant increase in SWS in the hypnosis condition. An additional control experiment excluded that mere expectancies or demand characteristics might explain our results. Thus, these control studies showed that the use of hypnosis and the content of the hypnotic suggestion are critical for the beneficial effect of hypnosis on SWS.

Interestingly, low suggestibles did not benefit from the hypnotic suggestions, but rather showed a descriptive tendency of reduced SWS after listening to the hypnotic suggestion, similar to our results in younger participants. Opposite effects of hypnotic suggestions in low suggestible have been reported in previous experimental studies (Jones & Spanos, 1982; Oakley & Halligan, 2013), raising the possibility that low suggestible participants are in fact (consciously or subconsciously) counteracting the given suggestions. As asking subjects to “simulate” the benefits of hypnotic suggestions on SWS can neither elicit the effect in low suggestible females (see Cordi et al., 2014), it remains an open question how elderly, low suggestible females could also benefit from hypnosis as a tool for SWS extension.

Generally, the amount of sleep and particularly SWS strongly decreases across the lifespan, and the decrease of SWS is paralleled by a loss of cognitive functions. While hypnotic suggestions might prove a relevant alternative to widely-utilized sleep medication, here we also show that the increase in SWS by hypnotic suggestions leads to significant improvement of prefrontal cognitive functions after the nap. More specifically, in the hypnosis condition we observed a 28% pre- to postsleep improvement in the verbal fluency task, which is assumed to strongly rely on the prefrontal cortex. This change was significantly higher as compared to the change observed in the control condition. Furthermore, a similar improving trend for memory consolidation the hypnosis-induced increase in SWS and SWA was also found. This pattern is well in line with the model proposed by Mander (2013) that low prefrontal SWA is associated with aging-related prefrontal atrophy and significantly contributes to prefrontal cognitive functions. Finally, the reported positive association between SWS, SWA and subjectively rated sleep quality confirms their contribution to the feeling of being rested and satisfied with one’s sleep.

While our study clearly shows that hypnotic suggestions are effective in extending SWS as well as cognitive functions in the elderly, there are limitations of our study. First, we only used female participants to control for possible increases in variance by gender differences in sleep architecture and hypnotic suggestibility. However, future studies will need to replicate the beneficial effects of hypnotic suggestion on SWS in men. Second, we examined only a midday nap, and it will be highly important to extend our findings to night-time sleep as well as sleep disturbances in the elderly.

Taken together, our results indicate that psychological interventions using hypnotic suggestions are effective in improving sleep and SWS as well as cognitive functions in the elderly. Our results suggest that hypnotic suggestions might prove a successful alternative for widely-used sleep-enhancing medication to extend SWS and improve cognition in the elderly. They provide an important basis for future studies examining the benefits of hypnotic suggestions in patients with sleep disturbances as well their long-term benefits after repeated applications in every-day life.

Methods

Participants

Forty-two healthy, German-speaking elderly females with a mean age (± standard deviation *[SD]*) of 67.10 ± 4.26 years (age range 60 - 82) took part in the experiment. Only females were recruited to avoid known gender effects on sleep architecture and suggestibility (Carrier, Land, Buysse, Kupfer, & Monk, 2001; Fukuda et al., 1999; Page & Green, 2007). One subject was excluded due to lacking sleep, two others did not keep caffeine restriction in one of the two experimental sessions. A prior power calculation based on our previously published study in young females (Cordi et al., 2014) revealed an optimal sample size of n = 38 participants to detect an effect size of $f = 0.33$ ($\eta_p^2 \approx 0.1$) with a probability of > 95% (assumed correlation among repeated measures $\rho = 0.4$, power calculation performed by G*Power3 (Erdfelder, Faul, & Buchner, 1996)). For the final sample of 39 subjects included in the analysis, suggestibility to hypnosis was scaled according to the Harvard Group Scale of Hypnotic Susceptibility (HGSHS) prior to the experiment (cut-off score for high suggestibility: HGSHS ≥ 7) (Bongartz, 1985). In this sample, nineteen women were highly suggestible (HS) (mean age 66.42 ± 4.10 years; HGSHS: 7.95 ± .20 *SEM*) and 20 women were low suggestible (LS) (mean age 67.70 ± 4.66 years; HGSHS: 4.03 ± .44). The two experimental groups did not differ in age ($p > .30$). Due to technical problems, memory performance data (paired-associates learning task) are missing for three subjects (2 HS, 1 LS). On average, participants reported normal sleep (Pittsburgh Sleep Quality Index, PSQI mean ± *SD*: 5.33 ± 2.60 (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989)). To assure general health of the subjects, a history of neurological or psychiatric disorders, intake of pharmacological sleep medication more than twice a month and acute physical disorders were defined as exclusion criteria. Participants were asked to refrain from caffeine and alcohol during the test day and to get up before 8 a.m.. Participants gave their written consent to take part in the study and were paid 140 Swiss francs for participation. The Ethics Committee of the University of Zurich approved the study.

Materials

Audio files. Participants either listened to a tape including hypnotic suggestions to sleep deeply or a control tape, both taken from Cordi et al. (2014). While hypnotic suggestions were given with a calming, soft voice and slow rate of speaking, the control text was as neutral as possible with neither activating nor calming words and an everyday intonation. Both texts are publicly available (http://www.psychologie.uzh.ch/fachrichtungen/allgpsy/biopsy/links.html). Participants were allowed to fall asleep during or after the tape, and were, in all conditions, constantly awakened after 90 minutes in bed (see Figure 1, for the procedure).

Memory measures. Two declarative memory tasks were performed before and after the nap. In the semantic verbal fluency test (SVT), subjects were asked to generate as many words of a given category as possible within 2 minutes. The number of acceptable, listed words was taken as measure of retrieval performance of long term memory storage (Lezak, 1995). This test has proven to be age-sensitive (Haugrud et al., 2010) and dependent on frontal functioning as shown in several lesion studies (Miceli et al., 1981; Ramier & Hécaen, 1970). For analyses, percentage of postsleep performance was computed relative to presleep performance. Parallel versions were used in a randomized order (four categories (animals, hobbies, fruits, professions) for pre-and postsleep measures in both sessions were used). As percentage of improvement across the nap strongly correlated with SVT performance before sleep ($r(45) = -.71$, $p < .001$ for hypnosis, $r(45) = -.52$, $p < .001$ for control), presleep performance was regressed out and the analyses were run on the adjusted values. Second, a word pair learning task (Rasch, Born, & Gais, 2006) was conducted. Hippocampus-dependent declarative memory consolidation of word-pairs is known to depend on early, SWS rich sleep (Plihal & Born, 1997; Rasch & Born, 2013). Subjects had to learn a list of 30 semantically related word pairs adopted from Rasch et al. (2006) and also used in Cordi et al. (2014), although presented more slowly (see Table S4). After a fixation cross, the first word appeared for 2 seconds, followed by a 500 ms blank interval and the second word, which was presented for 2 seconds. A blank interval of 500 ms preceded the next fixation cross. The words were presented in black font on white screen via E-Prime (Psychology Software Distribution, High Sittenham, UK). Each word was presented only once. Cued recall was tested immediately after learning and again after the nap. After the first word was displayed, participants were asked to come up with the corresponding second word aloud. Response time was not restricted. The order of the word pairs during recall differed from learning phase. Performance was measured as percentage of words recalled at postsleep retrieval relative to the number of word pairs remembered immediately after learning. In both declarative memory tests, parallel versions were used in a randomized order (for SVT, four categories (animals, hobbies, fruits, professions) for pre-and postsleep measures in both sessions were used).

Psychomotor vigilance test. After sleep, the psychomotor vigilance test (PVT) was conducted to overcome sleep inertia and measure the effects of sleepiness on vigilance (Dinges & Powell, 1985). A millisecond counter appeared on the screen at random intervals and subjects were asked to press the space key as soon as they recognized the counter counting upwards. The reaction time was displayed in ms for one second after the keypress.

Polysomnographic recordings. To measure sleep, electromyographic (EMG), electrocardiographic (ECG), and electroencephalographic (EEG) electrodes were attached. EEG was recorded using a high-density 128-channel Geodesic Sensor Net (Electrical Geodesics, Eugene, OR) with a sampling rate of 500 Hz. Impedances were kept below 100 kΩ. Electrodes were initially referenced against the Cz channel, however re-referenced during preprocessing to both mastoids. Data was preprocessed with Brain Vision Analyzer 2.0 (Brain Products, Gilching, Germany), filtering the data according to the standard filter settings suggested by the American Association of Sleep Manual (AASM), e.g., 0.3 – 35 Hz. Two independent sleep scorers blind to condition visually scored sleep in 30 second periods based on derivations F4, C4, O4, HEOG, VEOG, and EMG. In case of disagreement a third expert was consulted, who was also blind to experimental condition. Stages 1-3, REM sleep, and wake after sleep onset (WASO) were scored.

Power in slow-wave activity (SWA, 0.5-4.5 Hz) bands was computed for about 8-second epochs by a Fast Fourier Transforms (FFT) (using a Hamming window of 10% and a 0.2 Hz resolution) after excluding bad intervals marked by amplitudes exceeding power differences of 500 µV. Relative SWA with total power set to 100% was computed for the analyses. We focused on frontal SWA as this measure has been shown to be most relevant for sleep-related memory consolidation and cognitive functioning, particularly in the elderly (Rasch & Born, 2013, Mander et al., 2013). The electrodes were grouped to two topographical regions: right frontal (electrodes 1-5, 8-10, 14, 116-118, 124, 121- 123) and left frontal (electrodes 12, 17, 19-26, 28, 32-34, 38) region (see Figure S1). Frontal hemisphere (left, right) was used as factor in the ANOVA. Due to high correlations between SWA power in experimental and adaptation nights ($r(37) = .62$, $p < .001$), SWA amount of the adaptation night was partialed out of SWA in experimental sessions and the adjusted means were considered for analysis.

Design and procedure

Participants had an adaptation nap and two experimental nap sessions in the sleep laboratory. The experimental sessions were spaced 7 days apart, to control for an individual week schedule. Each week before both experimental sessions, subjects kept a sleep diary. All subjects were explicitly informed about the purpose to deepen their sleep through hypnosis. All sessions started around 1 p.m. with the attachment of 128 EEG electrodes, EMG and ECG electrodes, which recorded

the 90 minutes of nap including listening to the text before sleep in the experimental sessions. Before going to bed, participants performed two declarative memory tasks. When participants were lying in bed, lights were turned off and the 13 minutes tape record was started. Either the tape including hypnotic suggestions or the control tape was played over bedside speakers, in a randomized and balanced order according to a placebo-controlled cross-over design. After awakening, participants answered a subjective sleep quality questionnaire (Görtelmeyer, 2011) and conducted the PVT. Then they recalled the 30 word pairs before repeating the semantic verbal fluency test. At the end of the second experimental session, participants filled out a general post experimental questionnaire.

Statistical analyses. Sleep was analyzed using a repeated measures analysis of variance (ANOVA) using the repeated factor "text" (hypnosis vs. control) and the between subject factor "suggestibility" (high vs low). For EEG power analyses, the repeated factor "frontal hemisphere" (right, left) was additionally used. According to Fisher's protected LSD test, significant main effects and interactions were further explored using paired sample t-tests. Associations were explored with Pearson correlations. Using age as a covariate did not change the results. Means ± standard error of the mean (SEM) are shown unless otherwise indicated. The level of significance was set to $p = .05$.

Acknowledgements

We thank Brigitte Sonderegger, Sandra Aerne, Tamara Müller, Melissa Maeder, Mirjam Stieger, and Jasmin Widmer for assistance in data collection as well as Mick Lehmann and Thomas Schreiner for helpful comments. This work was supported by a Grant of the Swiss National Foundation (SNF) (PP00P1_133685), the University Research Priority Program (URPP) "Dynamics of Healthy Aging" and the Clinical Research Priority Program (CRPP) "Sleep and Health" of the University of Zurich.

Author contributions

B.R. and M.C. developed the study idea and designed the study. M.C. collected the data, S.H. and S.M. helped with the recruitment. B.R. and M.C. performed the data analysis. All authors contributed to data interpretation, manuscript drafting, and approved the final version for submission.

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Supporting Material for: Improving Sleep and Cognition by Hypnotic Suggestion in the Elderly

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Abbreviations: PAL: Word Pair Associate Learning Task; N1 and N2: Stage 1 and 2 sleep; SWS: Slow-wave sleep; REM: Rapid eye movement sleep; TST: Total sleep time; SWS latency: Slow-wave sleep latency, SWA: slow-wave activity

Supplemental Table S1. Sleep parameters for high (HS) and low suggestible (LS) subjects in both experimental nights

	HS		LS	
in % of TST	**Hypnosis**	**Control**	**Hypnosis**	**Control**
N1	12.10 ± 1.85	12.45 ± 2.23	13.87 ± 2.51	14.92 ± 3.46
N2	41.65 ± 3.69	44.67 ± 5.22	36.95 ± 4.31	35.80 ± 4.35
SWS	**27.48 ± 3.43**	**17.43 ± 4.03***	18.79 ± 4.47	24.36 ± 5.23
REM	0.14 ± 0.10	0.79 ± 0.79	1.02 ± 1.02	1.49 ± 1.05
WASO	18.58 ± 3.58	24.62 ± 5.98	29.34 ± 5.86	23.40 ± 4.59
In min				
Time in bed	89.79 ± 0.24	89.50 ± 0.28	89.41 ± 0.27	89.19 ± 0.25
TST	67.08 ± 4.90	66.45 ± 5.32	62.85 ± 4.90	68.55 ± 4.66
WASO	10.18 ± 1.76	16.84 ± 3.97	19.15 ± 3.67	15.35 ± 2.69
Sleep latency	21.71 ± 4.60	18.97 ± 4.44	16.75 ± 2.33	12.70 ± 2.94
SWS latency	**15.05 ± 3.61**	**27.66 ± 5.88***	25.58 ± 5.29	21.63 ± 5.38
REM sleep latency	67.34 ± 4.68	69.82 ± 4.53	70.45 ± 2.79	75.05 ± 2.93
SWA frontal	77.97 ± 2.07	74.79 ± 2.45	76.97 ± 1.98	78.10 ± 1.94

Notes. Values are means ± standard error of the mean. Stage 1 and 2 sleep (N1 and N2), slow-wave sleep (SWS), rapid eye movement sleep (REM), time awake after sleep onset (WASO), total sleep time (TST), slow-wave sleep latency (SWS latency), theta overall mean, and slow-wave activity (SWA) in parietal derivations. Significant differences are indicated by *$p \leq 0.05$

Supplemental Table S2. Memory performance in the semantic verbal fluency task (SVT) for high (HS) and low suggestible (LS) subjects in both experimental nights.

	HS			LS		
SVT	**Hypnosis**	**Control**	***p***	**Hypnosis**	**Control**	***p***
Pre sleep	17.58 ± 1.54	17.74 ± 1.13	.91	17.15 ± 1.61	16.95 ± 1.53	.91
Post sleep	18.47 ± 1.03	16.21 ± 1.03	.11	16.00 ± 1.19	17.25 ± 1.39	.29
% Change	**127.47 ± 16.95**	**95.37 ± 7.32**	**.056**	105.10 ± 11.28	116.29 ± 15.33	.57
% Change adj	**128.87 ± 10.22**	**97.33 ± 6.74**	**.015**	103.76 ± 9.82	114.44 ± 12.81	.53

Notes. Values represent means ± standard errors (SEM).

Supplemental Table S3. Memory performance in the word pair learning task (PAL) for high (HS) and low suggestible (LS) subjects in both experimental nights.

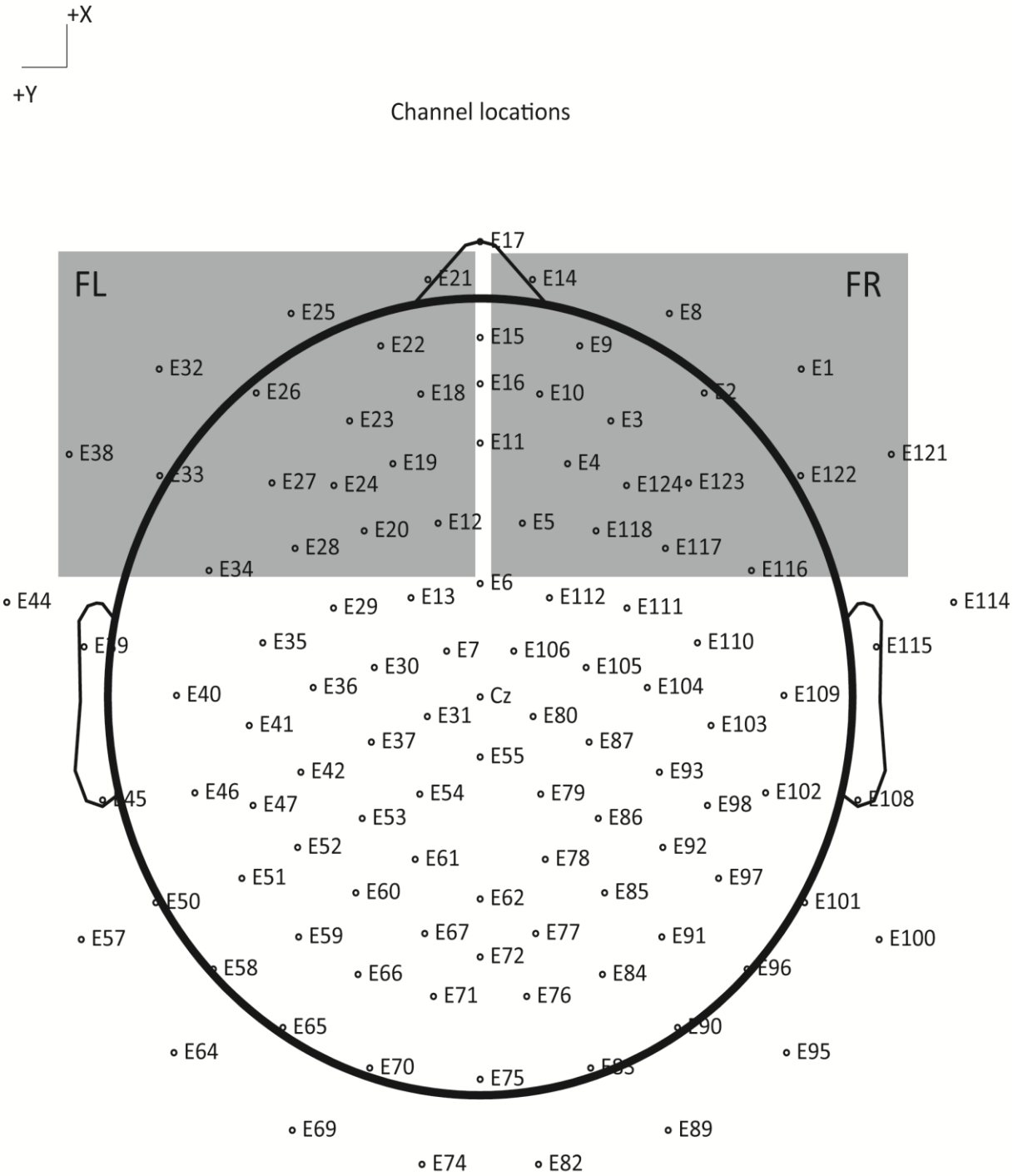
	HS		LS	
PAL	**Hypnosis**	**Control**	**Hypnosis**	**Control**
Pre sleep	14.82 ± .86	15.82 ± 1.27	15.84 ± 1.11	16.11 ± 1.47
Post sleep	13.18 ± .74	13.59 ± 1.24	13.84 ± 1.07	14.58 ± 1.34
% Change	89.70 ± 2.87	85.66 ± 3.86	87.08 ± 2.35	91.69 ± 2.78
% Change adj	89.70 ± 2.92	85.68 ± 3.89	86.91 ± 2.34	91.80 ± 2.70

Notes. Values represent means ± standard errors (SEM). All comparisons are non-significant (p > .10).

Supplemental Table S4. Parallel versions of the paired associate task (PAL) involved words, balanced according to concreteness, imagery, arousal, meaningfulness, association strength, frequency in use, and word length (Rasch et al., 2006).

Version A		Version B	
Word1	**Word2**	**Word1**	**Word2**
TRINKSPRUCH	SPRICHWORT	CHANCE	BEGEGNUNG
CHAOS	STRUKTUR	PLAN	GROSSSTADT
SKLAVE	KÖNIG	ZEIT	URSPRUNG
KUGEL	QUADRAT	ERDGESCHOSS	DACHBODEN
STURM	WINDHAUCH	PROFIL	PHOTOGRAPHIE
RÜSTUNG	ANGRIFF	BESITZ	ANTEIL
ANEKDOTE	WITZ	TÄUSCHUNG	ECHTHEIT
BEDÜRFNIS	WERBUNG	GEBÄUDE	HOTEL
MANGEL	VERZICHT	APFEL	PFIRSICH
SCHAMGEFÜHL	KÖRPER	TAT	ABSICHT
RÜCKSCHRITT	VERGANGENHEIT	AUTO	PRESTIGE
INFORMATION	INHALT	NORM	MORAL
NÄSSE	GEWITTER	DEFINITION	KONZEPT
ERDE	STEIN	SEGEN	SCHÖPFER
DEMOKRATIE	SYSTEM	GEIST	FLASCHE
BECHER	KAFFEE	FORDERUNG	GEHALT
STAUB	SAUBERKEIT	MEINEID	EHRENHAFTIGKEIT
URHEBER	KAUSALITÄT	INDUSTRIE	BRANCHE
FORM	KREIS	PUDDING	SÜSSIGKEITEN
FIGUR	BRETT	STOLZ	RUHM
VOGEL	KATZE	ZWIELICHT	UNTERWELT
BERUF	ANERKENNUNG	WOLLE	KLEIDUNG
BARGELD	WERT	VERGLEICH	GLEICHNIS
PELZ	FUCHS	ALKOHOL	OPIUM
SPASS	FEIER	BEWEIS	TATSACHE
STERN	WEIHNACHTEN	GESUNDHEIT	IMPFUNG
BEGRIFF	BEDEUTUNG	PAPIER	BRIEF
FÄHIGKEIT	VERANLAGUNG	GIFT	MORD
ZEITUNG	DRUCK	JUNGE	MÄDCHEN
PUPPE	KIND	ARMUT	ELEND

Supplemental Figure S1. Topographical regions defined for EEG data analysis. Two frontal areas were used: frontal left (FL), frontal right (FR).



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5. Discussion

The following sections will discuss the results of the three manuscripts presented. First, the most important findings will be summarized and embedded in literature. Data will then be interpreted in relation to previous work and implications will be drawn that will be further specified in the last section in terms of suggestions for future directions, derived from the present results and methods. Before providing an overview of the most important upcoming research questions arising from the current data, some limitations will be outlined.

5.1. The Role of REM Sleep for Memory Stability

Memory reactivations affect stability of declarative memories dependent on the brain state. During SWS, hippocampal replay stabilizes memories, while reactivations triggered during wakefulness destabilize memories. Previous human studies on neuronal reactivations during REM sleep mostly focused on procedural memories (Guerrien et al., 1989; Maquet et al., 2000), or did not specifically test for the stability of declarative memories after their reactivation during REM sleep (Rasch et al., 2007). The first manuscript has closed this research gap by investigating the effects of induced memory reactivations during REM sleep for memory stability.

In line with our hypothesis, cueing declarative memories during REM sleep did not benefit memory stability. This not only contradicts experimental findings of a beneficial role of REM sleep for memory, but also theoretical notions of a period of stabilization during REM sleep (Diekelmann & Born, 2010). In contrast, the wake-like electrophysiological and neurochemical character of REM sleep had given reason to expect a deteriorating influence of reactivations during REM sleep, but also these assumptions were not confirmed by the data, as cueing did not destabilize declarative memory either. This implies that hippocampal reactivations observed during REM sleep have no functional role for the stabilization of declarative memories. This conclusion finds further support in the fact that declarative memory stabilization had already been achieved after cueing during SWS in the study by Diekelmann et al. (2011). Possibly, reactivations only stabilize memories when SWS specific features are prevalent and thus, they have no stabilizing function when they occur during REM sleep. It could even be speculated that the replays observed in REM sleep are merely some kind of aftereffects of reactivations during SWS without any functional relevance. As data of several studies shows no impairment of declarative memory consolidation after lacking REM sleep (for an overview see McGrath & Cohen, 1978), it is also reasonable to assume that REM sleep generally has no

functional role for declarative memory. There are recent reviews that either deny a major role of REM sleep for memory consolidation (Siegel, 2001) or at least question its necessity and state uncertainty as to possible memory related mechanisms (Tononi & Cirelli, 2014). However, the nature of REM sleep actually entails characteristics that could be beneficial for memory processes. For instance, literature offers evidence that theta activity is critically involved in the strengthening of new memory traces (Poe et al., 2000) and the induction of LTP (Maquet, 2001; Pavlides et al., 1988). Further, theta power in REM sleep has been shown to contribute to the organization of firing patterns in terms of rate and synchrony during sleep, which hints at a fundamental role in physiological memory processes during sleep (Grosmark, Mizuseki, Pastalkova, Diba, & Buzsáki, 2012). It should be noted that these studies were based on animal research and, although quantitatively meager, patterns in humans are not fully in line with results in animals (Caplan, Madsen, Raghavachari, & Kahana, 2014). However, besides theta, also the neurochemical milieu during REM sleep offers advantageous conditions. For instance, ACh levels are assumed to influence the facility of neuronal activation spreading. While during REM sleep high cholinergic tone in hippocampal areas suppresses output from this region, relatively lower ACh levels in the neocortex enable communication and spreading of activation within associated neocortical networks (Cai, Mednick, Harrison, Kanady, & Mednick, 2009; Hasselmo, 1999; Payne, 2011). This expanding reciprocal activation favors the establishment of connections between similar memory traces and the formation of new networks. The symbiosis of new information and remote networks enables reorganization and the formation of new associative elements, the basis for creative problem solving (Cai et al., 2009; Landmann et al., 2014). Accordingly, Payne (2011) suggests that induced reactivations during REM sleep support restructuring and recombination of memory contents within neocortex which promotes insight and creative solutions. One conclusion arising from this notion is that new memories benefit during REM sleep if they can be connected to existing networks during this spreading activation period. Thus, beneficial effects of REM sleep for memory might be observable following an inverted u-shaped function of connectability between newly learned material and existing networks: If associations are already over-learned or too strong to elicit further linkage (comparable to a ceiling effect) or if no schema exists in which the newly learned material can be integrated, memories cannot benefit from REM sleep. However, remotely associated items might benefit the support of REM sleep by finding even distant connections to networks in which they can be integrated. These assumptions find evidence in the results of two studies. One study demonstrated improved problem solving after sleep versus wake for difficult, but not easy problems. It was concluded that in the case of easy problems, characterized by many associative links between stimuli and target word, activation was not required to spread widely to reach associable targets and thus can happen with or without sleep. On the contrary, those items with few associative links to

pre-existing networks need the support of sleep to spread widely enough to reach remotely associated links (Sio, Monaghan, & Ormerod, 2013). The second study showed a particularly enhanced priming effect for weakly associated word pairs compared to closely associated ones (Stickgold, Scott, Rittenhouse, & Hobson, 1999). Here, this difference only appeared after REM sleep periods, but not after NonREM sleep or wakefulness (Stickgold et al., 1999). It can thus be further concluded that particularly REM sleep enables widespread activation, which even allows remotely associated schemata to get connected. In short, reactivations during SWS might reflect the transmission of newly formed memory traces to neocortex while reactivations during REM sleep cause coupling and restructuring of transferred and remote memories (Payne, 2011).

Together, our data supports evidence attributing no functional role of REM sleep reactivations for memory stability. However, this does neither exclude other REM sleep features from contributing to memory formation nor a qualitatively different contribution of REM sleep reactivations to memory processing. Both possibilities should be further examined.

5.2. Influence of Hypnotic Suggestions on Sleep and Memory

Hypnosis has proven successful in reducing sleep impairments when measured with subjective reports. However, no attempts to confirm its influence on polysomnographic-based measures have been made. This thesis examined the efficacy of a hypnotic suggestion “to sleep deeper” in increasing the amount of polysomnographically measured SWS and SWA. Secondly, we expected declarative memory benefits of this increased sleep depth due to existing evidence on the role of SWS for memory consolidation.

Data in manuscript II even exceeded our expectations by showing an impressive SWS increase of 80% after a hypnotic suggestion to sleep deeper compared to the SWS amounts recorded after a neutral control text in highly suggestible females. These results also held for SWA, the electrophysiological hallmark of SWS: More power in the low frequency band was recorded during sleep after hypnosis than after the control text. It can only be speculated how this increase was achieved. According to Rainville and Price (2003), the hypnotic state is accompanied by a net activity decrease, characterized by higher synchronization and reduced cortical arousal. The modulated ascending activity paralleling relaxation might have initiated the calm down and allowed more restful sleep. Another possibility is that the increased theta activity, which appeared in highly suggestibles during listening to the hypnosis had contributed to the slowing of oscillations. This assumption is based on a study that investigated the electrophysiological markers of sleep homeostasis. During prolonged wakefulness, an increase in theta activity was recorded, a frequency band associated with

sleepiness (Strijkstra, Beersma, Drayer, Halbesma, & Daan, 2003; Torsvall & Åkerstedt, 1987). This increase in theta was related to enhanced power in slow-wave activity in the ensuing recovery sleep compared to a previous baseline night. Both effects were pronounced in frontal derivations, again hinting at its outstanding sensitivity towards wakefulness and need for recovery. Hypnosis might artificially have increased a sleep need by boosting theta activity during listening. This was compensated for by increased slow-wave activity during the NonREM period of the nap. The artificially high sleep propensity might also have contributed to the reduced time spent awake after first sleep onset in highly suggestibles after hypnosis. Increases in theta during hypnosis are in line with previous studies searching for electrophysiological correlates of the hypnotic state, particularly for highly suggestibles. This increase in theta was sometimes interpreted as reflecting elevated attentional processes and imagination (Galbraith, London, Leibovitz, Cooper, & Hart, 1970; Sabourin, 1990; Schacter, 1977). Differences in theta power also appear between highly and low suggestible subjects (Kirenskaya et al., 2011). Accordingly, also in our study low suggestibles did not show altered theta activity during hypnosis. In this group, also NonREM SWA was not increased either. In conclusion, it could be the relation between theta and its depletion through slow-wave activity which has evoked the enlargement of SWS.

The increase of SWS with hypnosis has several very special advantages compared to other interventions. One of the most precious advantages of SWS increase by hypnosis compared to pharmacological means is the specificity of the effect. The only reductions that paralleled the enhancement of SWS in our data were found in the amount of wakefulness after sleep onset. No sleep stage suffered from increased SWS. By comparison, SWS increases achieved with those few hypnotics that elevate instead of attenuate amounts of SWA (Lancel, 1999) are often accompanied by deteriorations of other sleep stages (Feld et al., 2013; Krueger, Kubillus, Shoham, & Davenne, 1986; Roth, Wright, & Walsh, 2006; Walsh et al., 2006). One of these studies did not even achieve SWS increases with lower doses of the medication and had to use a higher concentration to achieve any effect (Walsh et al., 2006). Higher doses, however, led to adverse side effects like decreases in subjectively rated quantity and quality of sleep, psychomotoric and attentional impairments (Roth et al., 2006; Walsh et al., 2006). In our study, SWS increases positively correlated with the increase in sleep quality and vigilance was not affected. Finally, besides high doses, pharmacological treatments might need up to several weeks to induce significant increases, while one single, 13 minute session of hypnosis was enough to achieve significant results (e.g., Sharpley, Attenburrow, Hafizi, & Cowen, 2005). Finally, exogenous chemical interventions might represent a disadvantage in the long run. Hypnotics usually provoke development of tolerance, forcing the consumer to increase the dose to maintain the level of effectiveness. For hypnosis as a more primal principle, the number of repetitions would be expected to rather act as a practice, easing generation of the hypnotic state and

enhancing efficacy with each trial. These comparisons hint at a more effective, unique, and qualitatively different, possibly more natural SWS enhancement when achieved by hypnosis compared to medication and should thus be taken seriously as an alternative approach to improve sleep. The long-term usage of hypnosis and the function of its efficacy over time must however still be tested, but theoretically hold a lot of promise.

What the dose of the hypnotics is for medication, the content of the metaphor is for hypnosis. Those highly suggestible subjects, who expected deep sleep suggestions while actually receiving hypnotic suggestions to make sleep more shallow, neither experienced an increase in theta nor in SWS or SWA despite the same induction procedure. This result signalized the decisive force of the content of the metaphor over success or failure of the intended effect. This is in line with its theoretical intention: The metaphor contains and transfers a certain message, which is sowed in the recipient to be processed and to elicit changes. Thus, it is the content of the metaphor which represents the actual intervention. What makes the approach so widely applicable is the fact that the message does not need to be consciously extracted and understood but only individually interpreted and accepted in order to take effect. Therefore, it does not require a certain competence on behalf of the subject to cognitively distract the meaning of the picture, but the mere absorption and openness towards the input. What surely supports not only the suggestion to be incorporated, but also the induction procedure to result in a deep hypnotic state is a high level of pre-existing expectations. When contradicting expectations are fuelled beforehand, the metaphor might not fall on fertile ground. This deliberately lacking - or wrong - preparation of the subject's expectations might limit the evolvement of the metaphor's power. Together, not only the content of the metaphor and the message it transfers must be very precise, but also the subject's expectancy and hope in the technique must be boosted. This is also reflected when regarding results of low suggestibles. Similarly to the control group, sleep could not be positively influenced in subjects who did not respond to hypnosis and might not have been convinced of its influence. To enable low suggestibles to also benefit from hypnotic suggestions it is important to test whether they simply need more confidence or training than highly suggestibles do or whether it might be helpful for them when the framing of the context is changed from hypnosis towards an imagination task. This strategy might minimize the risk of provoking internal resistance to manipulation and might foster compliance. Spanos et al. (1989) have already presented first results showing that the definition of the situation can be decisive whether the response to suggestion is facilitated or suppressed, depending on previous experiences and the attitude towards hypnosis. The dependency of the outcome on suggestibility again stresses the importance of taking this factor into consideration in experimental designs as well as in therapy.

After successfully increasing not only the amount of SWS, but also achieving changes in SWA, declarative memory consolidation was hypothesized to be improved according to theory. However, astonishingly, the tremendous effect on sleep did not influence memory consolidation. Possibly, young adults' night-time sleep already entails so much SWS that additional SWS in daytime naps does not add any memory benefit. This is however unlikely, particularly when comparing results to other studies which artificially increased SWS and SWA in younger adults, for instance by brain stimulation. The changes in amounts of SWS and power of slow oscillations were accompanied by improved performance in declarative memory test very similar to the one used in this thesis (Marshall, Helgadóttir, Mölle, & Born, 2006). What distinguishes the results of Marshall et al. (2006) from ours is the effect on slow spindle activity and spindle counts which was present in their data, but not ours. According to assumptions of Steriade and Timofeev (2003), spindle generation is involved in synaptic plasticity and also the active system consolidation theory states that it is the interplay between slow oscillations, spindles, and sharp-wave ripples which promotes the hippocampal-neocortical dialogue. It is hence plausible to reason that all three parameters must be increased to positively act on consolidation and that changes in spindle activity lacking in our data have hampered effects on memory consolidation. In line with this notion, one study pharmacologically increased SWS and SWA, but also failed to find positive effects on memory consolidation in the same memory task as used in our study. Of note, their medical intervention had decreased spindle activity (Feld et al., 2013). A pattern of unchanged spindle activity despite SWA increases appears astonishing when considering that Steriade and Timofeev (2003) argue that spindle generation is driven by slow oscillations. Consequently, one would expect changes in spindle activity as a consequence of elevated power in SWA bands. There is however evidence that < 1 Hz activity underlies different dynamics than delta waves above 2 Hz, both entailed in the SWA frequency range (0.5-4.5 Hz) (Achermann & Borbély, 1997). Thus, a separate consideration of slow oscillations (0.5-1 Hz) and delta activity (1-4.5 Hz) might be more revealing. Possibly, < 1 Hz power increase was too weak to influence spindles. This argues for analyses of thinner frequency bands. Additionally, future studies could try to influence spindle activity with hypnosis and combine it with SWS increases in order to alter memory consolidation.

Together, the results of the second manuscript impressively showed that the effect of hypnosis also extends to objectively measured parameters of sleep. Based on these results, positively influencing sleep by the application of hypnotic suggestions can be highly recommended. Data implies that in healthy sleepers, hypnosis can ameliorate sleep, a fundamental contributor to health and well-being. Diverse advantages of hypnosis compared to medical influences confirmed its natural, qualitatively different, and unique way of influencing sleep. First control groups uncovered

the importance of the content of the metaphor as well as suggestibility for the effect, but a deeper insight about underlying mechanisms should be gained. This could allow for broadening the application spectrum to more sleep parameters and push its influence on secondary factors such as memory. Thereby its potential could be leveraged for application. These investigations are worthwhile as hypnosis seems to be among the most effective, most widely applicable, easiest to implement and least risky methods to positively increase slow-wave sleep in humans.

5.3. Improvement of Sleep and Cognition by Hypnotic Suggestions in the Elderly

Due to the age-related decline in SWS amounts and accompanying losses in memory performance and subjective sleep quality, the results of manuscript II are highly important for older adults. Therefore, the study was replicated including an elderly sample in the third manuscript. According to evidence closely linking SWA, memory performance, and prefrontal functioning in older adults, benefits for prefrontal cognitive functioning were expected as well as for memory consolidation.

According to the hypotheses, hypnotic suggestions were successful in increasing the amount of SWS in a midday nap in highly suggestible older adults as well. Again, the effect was specific for SWS and was not to the significant detriment of other sleep stages. SWA power differed depending on text condition and suggestibility, resulting from a left frontal SWA increase after hypnotic suggestions in highly suggestibles. Comparisons to data collected in younger adults showed that the effects of hypnosis on SWS and SWA were independent from age. Thus, hypnotic suggestions positively influence sleep in young and old age to a comparable degree. Surrogates for medication that treats sleep problems are precious particularly for the elderly, who mainly resort to chemical means to improve their sleep quality. Statistics of health surveys indicate dramatic increases in the percentage of sleep drug users as a function of age. In the age range from 55 to 75, up to 8% of those questioned affirmed sleep medication intake in a survey conducted in Switzerland (SFA, 2009). The problems with this development are falls and hip fractures, which are associated with the use of hypnotics in elderly (Allain, Bentué-Ferrer, Polard, Akwa, & Patat, 2005), states of confusion and disorientation (Evans & Jarvis, 1972) and pronounced reductions in psychomotor functions in older compared to younger adults, as well as reduced feelings of being alert during the day (Castleden, George, Marcer, & Hallett, 1977). Such relationships clearly indicate that the usage of hypnotics should be decreased, particularly in older adults. Hypnosis has proven a promising alternative in the present thesis.

Our data additionally contributed evidence to the assumption that SWS and SWA benefit memory performance in PFC dependent tasks. Indeed, performance in the verbal fluency task, an age-sensitive (Haugrud, Lanting, & Crossley, 2010) and PFC dependent memory task (Benton, 1968; Milner, 1995) was more improved after SWS and SWA enriched sleep than after the control nap. Regarding SWA, increases in older adults were not as widespread as in younger adults, but recordable in the left frontal areas. A positive association between low frequency activity particularly in the left PFC during NonREM sleep and verbal fluency performance had already been reported by Anderson and Horne (2003). Our data supports this regional significance of the left PFC for verbal memory performance and suggests that deepened sleep might have restored frontal cortex function, leading to higher performance levels. These conclusions fit the model proposed by Wilckens et al. (2012), which assumes that age-related changes in SWS reduce prefrontal restoration, which impairs memory performance via limited executive control. As concrete measures of executive function were not available in our data, it is not inferable whether the obtained memory benefits were a consequence of improved executive control as assumed by the model or whether they were rather a direct consequence of a prefrontal benefit. Antonenko et al. (2013) also reported improvements in declarative memory performance after inducing slow oscillations during sleep in younger adults. However, working memory was not affected by the SWA increases, hinting at a direct rather than mediated influence of sleep on declarative memory performance. However, information about any correlations between SWA and memory performance in their data is not available. The lacking correlation between SWS or SWA increases and performance gain in our data at least suggests one or more mediating factors. PFC gray matter volume could represent a source of variance influencing the relationship between SWS/SWA and memory performance as well. The interdependency between those three parameters had previously been established (Anderson & Horne, 2003; Mander et al., 2013; Parkin & Walter, 1991). The inclusion of structural data in later studies could shed more light on its involvement.

Finally, our data provided evidence for the assumption that memory consolidation can be positively influenced by improved sleep. Memory consolidation after hypnosis-induced deep sleep was tendentially improved in highly suggestible subjects. In view of the lacking effect of sleep on consolidation in younger adults, this result was anything but predictable. One could argue that gains in slow-wave sleep only benefit memory when levels of deep sleep are generally low, as SWS amounts beneficial for memory can reach saturation. This could explain why only older adults benefit from more SWS, while young sleepers do not. However, despite other studies demonstrating memory consolidation benefits of manipulated sleep also in healthy younger sleepers (Marshall et al., 2004), there are studies in older adults which suggest a declining strength of the relationship between SWS and memory (Cherdieu et al., 2014; Hornung et al., 2005; Scullin, 2013). Based on such

studies, one would reject a saturation hypothesis in young adults and further expect relatively unchanged performance in declarative memory tasks after SWS-enriched sleep in older adults. Contrary to this, and in line with other studies (Aly & Moscovitch, 2010; J. K. Wilson et al., 2012), our data rather hints at preserved sleep-dependent declarative memory consolidation also in older age. In summary, on average, highly suggestible elderly subjects not only benefited from hypnotic suggestions in terms of increased SWS and SWA amounts, but also regarding cognition.

The positive correlation between SWS, SWA, and subjective sleep quality confirmed sleep depth to be an important target for the treatment of sleep complaints and subjective reports of poor sleep (Keklund & Akerstedt, 1997). Such relationships uncover the contribution of deep sleep and its slow oscillatory power for the feeling of being rested even in a 90 minute midday nap. Regarding the high prevalence of sleep complaints and their tight relation to comorbid health problems in older populations (Ancoli-Israel, 2009), there is urgent need for their treatment. Of note, sleep complaints must not necessarily be strongly related to objective poor sleep. Psychologically and physically healthy adults sometimes adapt their sleep quality rating to the one expected for increased age independent from objective impairments (Buysse et al., 1991). However, there is no reason to assume that sleep complaints without objective basis are less severe than those reflecting real sleep problems. In summary, even if no objective sleep impairment is present, sleep might subjectively suffer from age and negatively impact general feelings of health and well-being. Hypnotic suggestions to deepen sleep can be used to improve sleep objectively and subjectively and thereby reduce age-related complaints.

All in all, the results of the third manuscript replicated the effectiveness of hypnosis in an elderly sample. Additionally, data demonstrated the purview of the effects of hypnotic suggestions on objective and subjective measures of sleep and, importantly, on cognitive abilities. This implies that hypnosis takes effect independent from age and represents a non-drug alternative to treat sleep problems.

5.4. Limitations

The studies in this thesis also have to handle some limitations which will be outlined in this paragraph.

The way the experimental groups in study I were scheduled cannot control for circadian influences on performance. Due to the design of the night half paradigm, both the SWS and wake reactivation groups learned in the evening and recalled at about 0:30 a.m. while in our REM reactivation group, learning took place around 2:00 a.m. and recall followed in the early morning

hours. A session protocol that avoids possible influences of daytime has the SWS and wake groups stay awake until night-time, learn the card pairs at the same time as the REM sleep group and have their retention period until the early morning hours. Otherwise, the diverging circadian scenarios might be responsible for between-group performance differences. However, as comparisons of the effects of reactivations were done within each of the three groups, this does not affect the main conclusion that REM reactivations have not altered memory stability.

What limits generalizations from manuscripts II and III is the fact that we only tested females. In order to be able to make inferences on the general population, the study should be replicated in men. Although some studies found females to achieve higher scores in tests of suggestibility (Page & Green, 2007), others did not (Bongartz, 1985). Nevertheless, if men who are similarly highly or low suggestible as the women tested in our samples were recruited, we would have no reason to assume that they react differently on the hypnotic suggestions than our female participants. However, scientific evidence for this is lacking.

Another issue is that to ensure standardization, each subject received the same hypnotic suggestion played from an audio file. According to previously outlined case reports, individually suited metaphors would be expected to be even more effective (Stanton, 1999). Similarly, live hypnosis could be more efficient than a tape recording. In a therapeutical interaction, the hypnotist could for instance include tests to infer on the level of hypnotic depth before implementing the metaphor. In our setting this was not possible and thus, the metaphor was presented after the standard induction independent from depth of hypnosis. Despite the advantages of individually tailored metaphors and live sessions, these standardized settings were essential for our experimental purposes. However, now that the fundamental effect could be demonstrated and replicated, factors more relevant for practical application could be implemented at the expense of standardization.

5.5. Outlook and Integration of Findings

Data of the present thesis shed light on a theoretical and a practical aspect of the relationship between sleep and memory. The studies not only answered some previous questions, but also provided a basis for further investigations. This section will outline some issues worth being treated in some future studies.

New insights about the role of REM sleep for declarative memory consolidation were gained in the first manuscript. According to our findings, obtained by applying well established paradigms, spontaneous reactivations that occur during REM sleep do not contribute to declarative memory stability. The findings support previous evidence for spontaneous reactivations to change their functional significance for memory stability depending on the prevailing surrounding conditions that

hallmark the different brain states during which they appear, for instance, neurotransmitter concentration or electrophysiological events. This conclusion implies that the reasons for their functional difference must be found on a much finer level. Such investigations can be implemented by pharmacological manipulation of the neurochemical milieu or by electrical stimulation varying electrophysiology (Gais & Born, 2004; Marshall et al., 2006; Rasch et al., 2006). For instance, manipulating cholinergic tone during SWS and wakefulness uncovered its role as a switch between an encoding and a consolidation mode. While consolidation favors the low ACh levels prevalent during SWS, encoding requires the high levels present during wakefulness. Thus, so far, ACh was suggested as a mediator, determining whether consolidation is promoted or blocked (Hasselmo & Giocomo, 2006). However, as ACh levels during wake and REM sleep are comparably high, similar outcomes for the induction of reactivations in both brain states would have been expected, but do not correspond to our findings. Thus, ACh levels can at least not alone account for different effects of reactivations. Previously, different dynamics in theta and gamma activity as well as distinct levels of noradrenaline and serotonin were suggested to account for brain state dependent plastic changes (Tononi & Cirelli, 2014). Possibly their modulation, following the example set by those previous studies, could reveal further insight.

Another conclusion that can be drawn from comparisons with previous work is that the learning material is crucial for the findings. While for declarative memories, reactivations during SWS, but not REM sleep, act as stabilizers, this seems to be different for emotional or procedural memory (Guerrien et al., 1989; Hars et al., 1985; Maquet et al., 2000). Furthermore, when considering the notion that REM sleep reactivations cause memory reorganization and recombination (Landmann et al., 2014; Payne, 2011; Sio et al., 2013), the degree of the new material's connectability into existing networks could determine whether REM sleep benefits memory by promoting those connections or not. It could be hypothesized that particularly low associable material requires support in order to get integrated into existing networks and hence benefits from REM sleep reactivations, while easy to integrate or items which cannot be linked to any network do not. To test the assumption, the remote associations test (RAT) as used by Sio et al. (2013) could be applied. This test requires coming up with a word that is associated with three given words (e.g., lick, sprinkle, mine; target word: salt). Stimuli with close versus distant connections to the target word manipulate task difficulty and thereby determine how widely activation must expand to get any connection. Sio et al. (2013) compared sleep to wake groups and revealed better performance in the sleep group for difficult items. Thus, sleep has promoted the establishment of connections for low associable items. To test whether REM sleep reactivations are responsible for this effect, half of the difficult problems which remained unsolved before sleep could specifically be reactivated during REM sleep. The comparison of the

amount of problem solving after sleep in reactivated versus non-reactivated trials could uncover the role of REM sleep reactivations for the integration of low associable items.

Besides dependency from item connectability, REM sleep might promote changes that are rather qualitative in nature in contrast to quantitatively measureable changes after SWS. Thus, measuring reorganization and integration might require different tests than transfer and stabilization. As an alternative to tasks requiring creative problem solving such as the RAT, recall strategies, false memories, or position effects at recall could represent examples for measures that possibly allow for inferences on cognitive reorganization and integration.

In the course of inducing reactivations during several sleep and wake states, it must be noted that reactivating memories during the hypnotic state is still pending, although highly promising. Due to being highly focused and receptive during hypnosis, input given in this state possibly enjoys a particular kind of processing which might benefit retention. One could argue that regarding the increases in theta and alpha prominent to be elicited during hypnosis, this state rather resembles REM sleep or wakefulness for which no or even negative effects for memory stability have been shown. However, as theta rhythm induces LTP (Maquet, 2001; Pavlides et al., 1988), reactivations during hypnosis could represent a highly beneficial learning or processing background. Besides, this test would perfectly align in the first manuscript as a control group for the waking condition. While SWS and REM reactivation groups compared effects of low versus high levels of ACh, comparing wake and hypnosis reactivation groups could test the influence of the encoding mode, which was suggested to be involved in memory destabilization that followed cueing during wakefulness. While prefrontal activation during reactivation in the wake state suggested active re-encoding of cued memories, attention is very focused and limited during the hypnotic state. Consequently, it would be expected that updating of reactivated items that possibly happens during wakefulness and disturbs memory stabilization is reduced or even absent during hypnosis, as it is during sleep. Thus, keeping ACh levels constant, the influence of the encoding mode could be tested in this comparison.

After the first manuscript had confirmed that reactivations particularly stabilize memories during SWS, both last manuscripts uncovered the potential of hypnotic suggestions to increase the amount of SWS in younger and older adults. Thus, to add their beneficial effects, reactivations could be induced during SWS after having increased the amount of SWS with previously presented hypnotic suggestions. As it was sometimes shown that the duration of SWS correlates with performance improvements (Takashima et al., 2006), it could be assumed that memory benefits increase dependent on the duration of reactivations and render effects on memory consolidation significant.

Besides amounts of SWS, subjective sleep and - in older adults - prefrontal functioning were improved after hypnotic suggestions. These findings hopefully stimulate further research on hypnosis

and its impact to improve sleep and cognitive abilities across lifespan. Apart from further interesting investigations about the underlying mechanisms, several practical questions persist. The most important issues that should be followed up on are the degree of effectiveness in sleep disturbed patients, long-term effects, and the measurement of effects outside laboratories. Although very large effects appeared for both healthy groups, changes might be harder to achieve in a sample suffering from clinically relevant sleep disorders. This could be due to a heterogeneous nature of the sleep problems. If diverse aspects of sleep are affected by a disease, a specific intervention focusing on SWS as intended with the currently used suggestion might not be comprehensive enough to achieve observable effects. This does, however, not rule out other metaphors from having beneficial effects. The currently used metaphor to deepen sleep should however be tested in a sample of patients specifically suffering from SWS reductions to achieve significant improvements.

Only ongoing measurements of SWS amounts can capture the benefit`s function over time. Thus, longitudinal follow-ups should be set up to investigate the development of hypnotic effects in long-term applications. The ease of achieving the hypnotic state would be expected to increase with "training". A more stable and deep hypnotic state could be an even better background for the absorption of hypnotic suggestions and might increase also their efficacy. Therefore, the long-term treatment with hypnotic suggestions would be supposed to multiply the effect size. For older adults, this would possibly imply even more pronounced cognitive benefits. This investigation aims at providing an easy to implement, cheap, and low-risk possibility to treat sleep problems across a longer period of time. As such an intervention should take place at the patients' homes instead of laboratories, it would be crucial to previously clarify how the effects of hypnosis on sleep behave in an ecologically valid setting. To approach an everyday life scenario, the current study must be replicated in the subjects' private bedrooms instead of sleep laboratories and in whole nights instead of naps. Testing whole night recordings is particularly crucial as it could be well assumed that effects decline across a sleep period that is longer than our 90 minutes nap and thus become irrelevant in whole night recordings. This would also render long-term treatments questionable. One could however argue that regarding the specifically beneficial role of the first NonREM period for memory as shown by Anderson and Horne (2003), it could nevertheless positively influence cognition and hence worth being investigated. Moreover, a way to extend hypnotic effects across a longer sleep period is conceivable. Reactivating hypnotic suggestions during sleep by replaying short parts or single words of the hypnotic suggestions could retrigger relaxation and oscillatory power increases in later parts of the night. Of note, although conscious memory is often blurred for the exact content of the spoken words during the hypnotic procedure, cues are also supposed to work even when they were established unconsciously. Otherwise, in order to avoid risks of powerless cues, a less specific reactivation could be applied by using odors as a means for cueing. Using odors to trigger

reactivation would be less vulnerable to the risk of cueing certain words of the hypnotic text which the patient did not focus on or even had rejected for his personal mental travel and hence are not able to reactivate the relaxing state. Representing the same odor during sleep as during previous hypnosis could less specifically cue the whole hypnotic setting. As in this case, not the transfer to long-term storage, but the wide activation of associated patterns is intended, and cueing of hypnotic suggestions could be most effective during REM sleep. This assumption is based on the theory that activation spreads through networks particularly easily during REM sleep. Thus, initiating activation in this sleep stage might most likely reach the most widespread reactivation in networks, which were active during hypnosis.

Finally, the question of for how long the improvements are measurable when the application is discontinued after certain weeks of treatment remains. Possibly, one's bedroom gets associated with the effect of the hypnosis over time and automatically triggers deep sleep similarly to classical conditioning. If conditioning worked, benefits could persist without continuous treatment and become a naturally occurring mechanism.

To sum up, the results of the three manuscripts included in this thesis answered open research questions and provided a scientific base for deriving further interesting research questions. The methods introduced and applied in the course of this work proved purposeful and rewarding.

5.6. Final Summary

Sleep is critically involved in aspects of health, well-being, and cognition. The underlying mechanisms are however still elusive and hence extensively investigated. Knowledge arising from this thesis contributes to the basic understanding of this relation by providing a basic insight into the association between REM sleep and memory consolidation. In addition, the thesis provides an applicable tool to improve sleep and boost memory performance by providing first objective evidence for the effectiveness of hypnotic suggestions to increase sleep depth and sleep quality. New conclusions can be derived from these manuscripts that impact on future research and hopefully stimulate further investigations as well as practical applications. First, REM sleep reactivations play no functional role in the stabilization of declarative memories. Thus, it is implied to examine their behavioral relevance on a more finely-tuned level and with diverse memory tasks. The second and third manuscript provided objective evidence for the effectiveness of hypnotic suggestions to increase the amount of polysomnographically measured SWS and SWA. Effects in younger adults could be replicated in an elderly sample. Accompanying improvements in cognitive performance

underlined the importance of high levels of sleep quality across lifespan. This low-risk, non-pharmacological and easy to implement intervention thus proved worthy of being investigated in more detail to understand its mechanisms and extend its applicability. The present data lay the foundation for further studies aiming at broadening the usability of hypnotic suggestions by conducting whole night and long-term studies as well as by replicating findings in a clinical sample. In addition, a combination of hypnotic suggestions and induced reactivations is conceivable to keep the hypnotic effect constant across an extended sleep period, to enlarge time spent in SWS so that more reactivations can be induced or to reactivate memories in a particularly receptive brain state. The findings and methods of the manuscripts embedded in this thesis thus offer an untapped potential to positively influence deficits in integral areas of life as health and well-being and should therefore be further applied and extended.

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7. Curriculum Vitae

MAREN JASMIN CORDI

Curriculum Vitae

- September 2014 -

CONTACT INFORMATION

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PERSONAL DATA

Born: 26.08.1986 in Nürtingen

Citizenship: German

EDUCATION AND DEGREES

since 2012 **University of Zurich, Department of Biopsychology, Switzerland**

PhD student, enrolled in the PhD program

Doctoral thesis: “Improving sleep and cognition in young adults and elderly”

Supervisors: Prof. Björn Rasch, Prof. Dr. Mike Martin

Member of the peer mentoring group “Applied Programming for Psychologists”

2006-2012 **Eberhard Karls University of Tübingen, Germany**

Diplom Psychologin (Univ.)

Major subject Psychology; Minor subject Criminology

Diploma Thesis: „Memory belief: Lifespan age differences and its relation to episodic memory performance“.

Supervisors: Prof. Rolf Ulrich, Dr. Yee Lee Shing, Dr. Yvonne Brehmer

1997-2006 **Hölderlin Gymnasium Nürtingen, Germany**

RESEARCH INTERESTS

- Aging processes (memory, e.g., Dementia; intervention, memory training)
- Sleep's role for memory
- Memory formation and processes
- Influence of hypnosis (on sleep and memory)

PERSONAL EXPERIENCE

May 2011 - Sept 2011 **Internship at the University of Zurich, Department of Biopsychology (Prof. Dr. Björn Rasch), Switzerland**

Planning and implementation of an EEG study, data collection, preparation and analyses

Jan 2010 - Mar 2010 **Internship at the Max Planck Institute for Human Development, Berlin, Germany**

Assistance in the research project CONMEM: organization and coordination of the measurements, recruiting and data collection in younger and older subjects.

Investigation of an own project within the study resulting in the diploma thesis

Oct 2009 - Dec 2009 **Internship at Schütz & Hirsch, market research, Stuttgart, Germany**

Research, construction of questionnaires, recruitment of subjects

Feb 2009 - Apr 2009 **Internship at the Milton Erickson Institute, Rottweil, Germany**

Organization and administration of hypnosis courses and therapies as well as participation in the workshops

TEACHING EXPERIENCE

02/2013 – 06/2013 Seminar "Sleep and Memory" for Masterstudents, Department of Biopsychology, University of Zurich

MANUSCRIPTS

Cordi, M.J., Schlarb, A.A., Rasch, B. (2014). Deepening sleep by hypnotic suggestions. *SLEEP*, 37(6): 1143-1152.

Cordi, M.J., Ackermann, S., Hartmann, F., Konrad, B.N., Genzel, L., Pawlowski, M., Steiger, A., Rasch, B., Dresler, M. (2014). On lunar effects in sleep and the file drawer problem. *Current Biology*, 24(12):549-550.

Cordi, M.J., Diekelmann, S., Born, J., Rasch, B. (2014). No effect of odor-induced memory reactivation during REM sleep on declarative memory stability. *Frontiers in Systems Neuroscience*, 8 (157). doi: 10.3389/fnsys.2014.00157.

Cordi, M.J., Hirsiger, S., Mérillat, S., Rasch, B. (submitted). Improving sleep and cognition by hypnotic suggestion in the elderly.

CONFERENCE PRESENTATIONS

Cordi, M.J., Schlarb, A.A., Rasch, B. (2014). Deepening sleep by hypnotic suggestions. *SLEEP*, 37(6): 1143-1152.

Talk at the 34th International Hypnosis Congress, Berlin, Germany and posterpresentation on the 39th conference “Psychologie und Gehirn” in Würzburg, Germany.

Cordi, M.J., Hirsiger, S., Mérillat, S., Rasch, B. (submitted). Improving sleep and cognition by hypnotic suggestion in the elderly.

Posterpresentation on the 49th conference “Psychologie und Gehirn” in Lübeck, Germany.

ACADEMIC SUPERVISION

2013-2014	Sandra Aerne (Master thesis)
2012-2013	Isabelle Braham (Master thesis)
	Pascal Kröni (Master thesis)
	Fatime Bislimi (Master thesis)
	Tamara Müller (Master thesis)
2011-2012	Sandra Perner (Master thesis)

2012-2014 Interns: Tobias Egli, Benjamin Roth, Andrea Schmidt, Mirjam Stieger, Melissa Maeder, Jasmin Widmer, Maya Schenker, Amela Kujevic

GRANTS

October 2013	Travel Grant for participating at the Hypnosekongress 2013 in Berlin.
August 2014	Wissenschaftspreis 2014; Deutsche Gesellschaft für Zahnärztliche Hypnose (DGZH) e.V. for the work „Hypnotische Suggestionen vertiefen den Schlaf“

OTHER

Languages

English: fluently

French: good knowledge

Spanish: basic knowledge

EDV

Power Point, Word, Excel, SPSS, Brain Vision Analyzer: profound knowledge

R, Matlab, EEGLAB, E-Prime: basic knowledge

Zürich, September, 2014